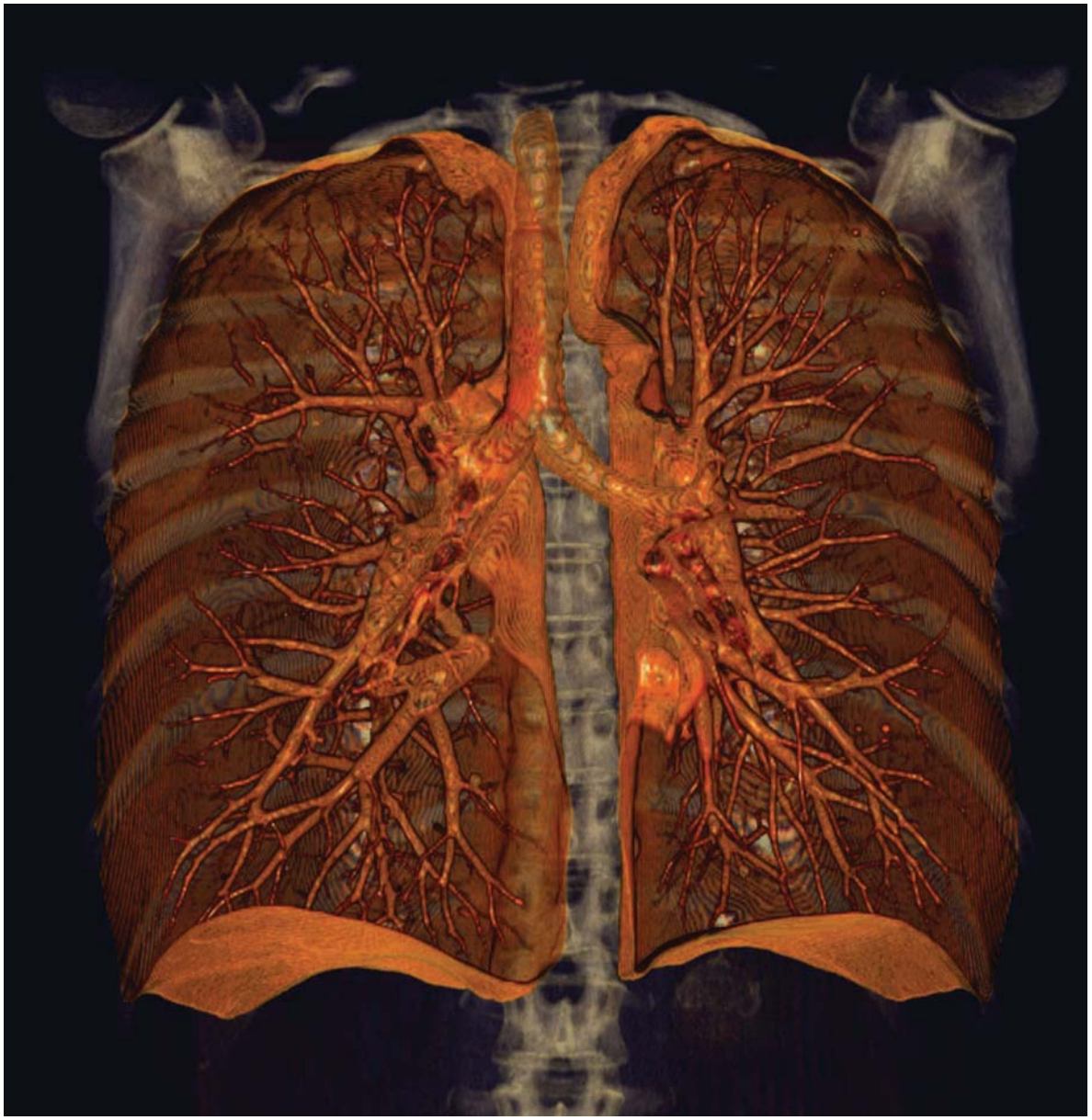
Health Protection Agency

Risk of Solid Cancers following Radiation Exposure: Estimates for the UK Population

Report of the independent Advisory Group on Ionising Radiation



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Foreword

There is understandable concern about the risks to health of ionising radiation arising from natural and man-made radioactive materials, including medical X-rays. In 1995 the Director of the then National Radiological Protection Board (now part of the Health Protection Agency) set up an Advisory Group on Ionising Radiation (AGIR):

> 'to review work on the biological and medical effects of ionising radiation relevant to human health in the occupational, public health, medical and environmental fields and advise on research priorities'

The Health Protection Agency (HPA) has a statutory responsibility for advising UK government departments and others on health effects of radiation and appropriate standards of protection. The AGIR is an independent body reporting to the HPA Board. Full details of the current work of the AGIR can be seen at www.hpa.org.uk.

This report is one of nine prepared by the AGIR and its subgroups set up to focus on specific topics. It covers the risk of ionising radiation on the development of 'solid' cancers such as cancers of the lung, prostate and breast, but excludes cancers such as leukaemia and lymphoma.

The specific remit of the Subgroup on Solid Cancer Risk was to review information on the risk of solid cancer following exposure to ionising radiation and to derive risk estimates for the UK population, taking into account uncertainties in the estimates. This report complements an earlier AGIR report entitled *Risk of Leukaemia and Related Malignancies following Radiation Exposure*, published in 2003. The two reports taken together therefore provide a comprehensive description of the risks of cancer due to ionising radiation exposure in the UK. As with the other AGIR subgroups, the objective was to provide scientific assessment and interpretation, not to make recommendations relating to radiological protection policy – these are matters for which the HPA and its Board are responsible.

The report is necessarily detailed and comprehensive. The introduction (Chapter 1) gives basic information on ionising radiation, how it is measured and how risks to various parts of the body are assessed. Chapters 2 and 3 give the scientific detail, and Chapter 4 focuses on the radiation risks to the UK population including methodological aspects of how risk is quantified, with examples of the risk for specific screening activities, such as mammography screening for breast cancer and CT scanning of the heart for ischaemic heart disease. Chapter 5 provides a brief overall summary with conclusions. A glossary is provided and details of the calculation of radiation risks are given in the appendices.

Risk of Solid Cancers following Radiation Exposure: Estimates for the UK Population

HAS BEEN PREPARED BY THE

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Risk of Solid Cancers following Radiation Exposure: Estimates for the UK Population

Report prepared by the Subgroup on Solid Cancer Risk of the independent Advisory Group on Ionising Radiation

Chairman of Subgroup: Professor Sir Nicholas Wald
Chairman of Advisory Group: Professor Bryn Bridges OBE

This report from the independent Advisory Group on Ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

1 Introduction

The Subgroup on Solid Cancer Risk of the independent Advisory Group on Ionising Radiation (AGIR) was established in 2005 to review information on the risk of solid cancers following exposure to ionising radiation and to derive risk estimates specific for the UK population. The report evaluates information on the risk of radiation-induced solid cancers in the organs and tissues of the body and develops advice on dose–response relationships for the UK population.

1.1 Ionising Radiation and How We Are Exposed to It

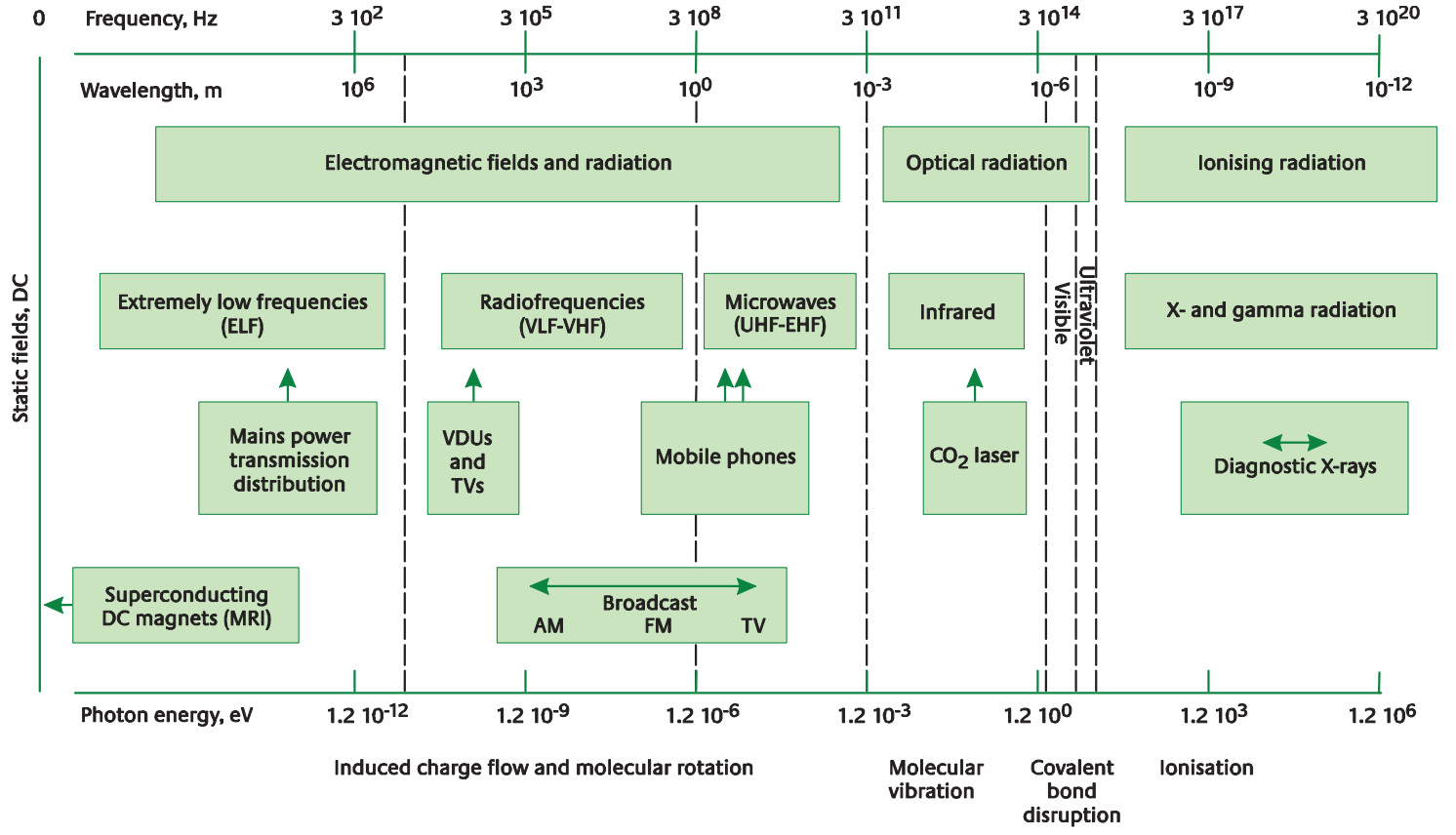
The human population is exposed to a wide range of different radiations. They are classified according to the effects they produce on matter and living material. There are two categories, ionising radiation and non-ionising radiation. Ionising radiation arises from natural and man-made radioactive materials and includes cosmic rays, X-rays, neutrons and the radiations emitted from radioactive materials including alpha (α) and beta (β) particles and gamma (γ) rays. The deposition of energy causes ionisation in the cells and tissues of the body.

Non-ionising radiation comes from sunlight, power lines, electrical equipment and mobile telecommunications systems amongst other sources. It does not deposit sufficient energy in the body to produce ionisation in body tissues. Information on the health effects of exposure to non-ionising radiation has been reviewed elsewhere (AGNIR, 2002; NRPB, 2004). Figure 1.1 illustrates the different types of radiation in the electromagnetic spectrum.

Ionising radiation is produced in the environment because of the presence of naturally occurring radioactive minerals remaining from the very early formation of the planet. This leads to exposure to gamma rays and to the radioactive gas radon and its decay products originating from uranium in certain rocks and from other radioactive material in our food and drink and in the general environment. Cosmic radiation comes from outer space and passes through the atmosphere of the planet.

There are three main sources of exposure to man-made ionising radiation. It is used in medicine for treating cancer and for the diagnosis of many diseases. Radioactive materials are used in industry, primarily for measurement purposes, and in the nuclear power programme for producing electricity. Both medical and industrial uses produce radioactive waste. Man-made ionising radiation is also present as fallout from nuclear weapon explosions and from other accidents and incidents worldwide, such as the Chernobyl nuclear plant accident on 26 April 1986. Exposure of the UK population to man-made ionising radiation from medical and industrial uses is closely monitored and controlled.

The quantity used to define the amount of radioactivity present is the becquerel (symbol Bq).
One becquerel of a radionuclide produces, on average, one radioactive decay per second. However,



Hz = hertz
m = metre
eV = electron volts

DC = direct current
VDU = video display unit
TV = television

AM = amplitude modulation
FM = frequency modulation

ELF = extremely low frequencies
VLF = very low frequencies

VHF = very high frequencies
UHF = ultra high frequencies
EHF = extremely high frequencies

FIGURE 1.1 Electromagnetic spectrum

radioactive decay is a random process, so if 1 Bq is measured for 100 seconds, the number of decays measured would probably be between about 80 and 120. If the measurement was to be repeated many times the average result would be close to 100. Submultiples or multiples of the becquerel are also used, such as the millibecquerel, mBq, which is one-thousandth of a becquerel or the kilobecquerel, kBq, which is 1000 becquerels (see Table 1.1).

When ionising radiation passes through matter it deposits energy which causes ionisation to occur and this can result in chemical changes to biological molecules and, as a result, cause damage to organs and tissues. The amount of energy deposited is called the *absorbed dose;* it is expressed in a unit called the gray, symbol Gy, where one gray is equal to one joule per kilogram. Submultiples of the gray are also used, such as the milligray, mGy, which is one-thousandth of a gray, or a microgray, μGy, one-millionth of a gray (Table 1.1).

TABLE 1.1 Radiation quantities and units

Quantity	**Symbol**	**Unit**	**Symbol**
Activity	–	becquerel	Bq
Absorbed dose	D	gray	Gy
Equivalent dose	H_T	sievert	Sv
Effective dose	E	sievert	Sv

Prefixes					
k	kilo-	thousand	m	milli-	thousandth
M	mega-	million	μ	micro-	millionth
G	giga-	thousand million	n	nano-	thousand-millionth
T	tera-	million million	p	pico-	million-millionth

Ionising radiations differ in the way that they interact with biological materials and cause damage so that equal absorbed doses (ie equal amounts of energy deposited) do not necessarily have equal biological effects. Radiations may have a low rate of loss of energy per unit track length and be termed low linear energy transfer (LET), as for X-rays, gamma rays or beta particles; or they may have a high rate of loss of energy and be termed high linear energy transfer, as for alpha particles and neutrons. The biological effects of high LET radiations are in general much greater than those of low LET radiations with the same energy. This is because high LET radiation can deposit most of its energy within the volume of one cell of the body and the chance of damage to the cell DNA is therefore larger. In order to equate exposures to different types of radiation the absorbed dose is conventionally multiplied by a *radiation weighting factor*, symbol w_R, which takes account of the different abilities of various radiations to cause

late health effects such as cancer. Values of w_R have been defined by the International Commission on Radiological Protection (ICRP, 2007). Thus for X-rays, gamma rays and beta particles the w_R is taken to be 1 and for alpha particles it is 20 (Table 1.2). The absorbed dose multiplied by the appropriate w_R value is termed the *equivalent dose* with the unit of sievert, symbol Sv. Defined in this way, the equivalent dose provides an index of the risk of harm to a particular organ or tissue from radiation exposure, regardless of the type or energy. Thus 1 Sv of X-rays would be expected to have a similar effect to 1 Sv of alpha particles. Submultiples are also used, such as millisievert, mSv, and microsievert, μSv.

TABLE 1.2 Radiation weighting factors recommended by the ICRP in Publication 103 (ICRP, 2007)

Radiation	w_R
Photons	1
Electrons, muons	1
Protons, charged pions	2
Alpha particles, fission fragments, heavy ions	20
Neutrons	A continuous function of neutron energy

The risk to the various parts of the human body varies between organs and tissues. At low radiation doses the main effects of concern are radiation-induced cancer caused by direct damage to body tissues and genetic disease resulting from damage to the germ cells in the male and female gonads. To allow for the varying sensitivity of organs to the induction of radiation effects, the ICRP has developed *tissue weighting factors*, w_T, which allow for these differences in radiation detriment (ICRP, 2007). Thus the lung and bone marrow are particularly sensitive to the induction of lung cancer and leukaemia and have a w_T of 0.12. In contrast, the cells on bone surfaces and the skin have a low sensitivity to the induction of cancer and are given w_T values of 0.01 (Table 1.3). The sum of all the w_T values equals 1. Multiplying the equivalent dose to each organ or tissue by the appropriate w_T value and then summing across all the organs and tissues of the body gives the *effective dose*.

The quantity effective dose is valuable for use in radiological protection and allows doses from partial- and whole-body exposure as well as doses from external radiation and from intakes of radionuclides to be summed and compared with dose limits. However, the quantities w_R and w_T are rounded values and the quantity effective dose does not provide information on doses to individual organs and tissues, which may be very variable. For epidemiological studies, therefore, the tissue absorbed dose is the most useful metric for quantifying exposure. In addition, w_T values are based on estimates of radiation detriment that are derived from the risks of radiation-induced cancer and genetic disease. The effective dose is therefore inappropriate for assessing risks of high doses of radiation that cause severe tissue reactions such as cell killing.

Estimates of the radiation exposure of typical members of the UK population from all sources of ionising radiation are given in Table 1.4 (Hughes et al, 2005; Watson et al, 2005). The total mean annual radiation dose from all sources is estimated to be 2700 μSv (2.7 mSv). On average, doses from occupational exposure and nuclear weapons fallout make up less than 1% of the total, doses from medical use in diagnosis are about 15% and the remainder (about 84%) comes from natural sources, predominantly from indoor exposure to radon and its decay products. Similar figures are seen in other economically developed countries. Doses from radon vary widely across the country depending upon the underlying rock structure. The highest levels tend to be found in southwest England. Thus average levels of radon in UK homes are about 20 Bq m^{-3} but average levels in Cornwall are about 100 Bq m^{-3} with a few houses above 10,000 Bq m^{-3}. Levels in the UK tend to be lower than those in many other European countries.

TABLE 1.3 Tissue weighting factors recommended by the ICRP in Publication 103 (ICRP, 2007)

Tissue	w_T	Σw_T
Bone marrow (red), colon, lung, stomach, breast, remainder tissues*	0.12	0.72
Gonads	0.08	0.08
Bladder, oesophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04

* Remainder tissues: adrenals, extrathoracic (ET) region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate, small intestine, spleen, thymus and uterus/cervix.

TABLE 1.4 Annual exposure of the UK population from sources of ionising radiation (Hughes et al, 2005)

Source		Mean annual effective dose (μSv)	Total (%)
Natural	Cosmic	330	12
	Gamma	350	13
	Internal	250	9.5
	Radon	1300	50
Man-made	Medical	410	15
	Occupational/industrial	6	0.2
	Weapons fallout and Chernobyl	6	0.2
	Discharges	0.9	<0.1
	Consumer products	0.1	<0.1
Total (rounded)		**2700**	**100**

Thus the typical value for Germany is about 50 Bq m^{-3} and for the Republic of Ireland 90 Bq m^{-3}. The AGIR has recently reviewed information on the consequences of exposure to radon (AGIR, 2009a; see Table F1 of that report for estimates of effective dose from radon exposure in the UK based on a variety of assumptions).

1.2 Risks of Radiation Exposure

The damaging effects of ionising radiation come from the packages of high energy that are released from radioactive material. Although different types of ionising radiation have different patterns of energy release and penetrating power, there is no general property that makes man-made ionising radiation different and more or less damaging than the ionising radiation that comes from natural radioactive material. This means that we can make direct comparisons between doses from man-made sources of ionising radiation and those from natural sources.

The effect of radiation on the human body depends upon a number of factors including:

a the radiation dose,

b whether it is from external exposure or from intakes of radioactive materials,

c its distribution in the body and the time period over which it is received,

d the sensitivity of the individual exposed, which can be influenced by both sex and age.

High radiation doses, above about 1 Sv received in a few minutes or hours can cause early effects, mainly due to cell killing, within a few days or weeks of exposure. In severe cases, above several sievert, this can lead to death of the exposed individual. At doses lower than around 1 Sv and for exposures over days, weeks or even years, damage may become manifest many years after radiation exposure. Radiation-induced cancer can occur in exposed individuals and radiation-induced genetic disease in their descendants. It is generally assumed that any radiation exposure can cause these late effects, although the probability depends upon the radiation dose and the dose rate.

Most quantitative information on the risks of cancer comes from populations that have been exposed to high doses and high dose rates. It is generally accepted that at low doses and low dose rates the risk of exposure will be reduced. As a consequence, a reduction factor, termed by the ICRP a *dose and dose rate effectiveness factor* (DDREF), has been applied to the risks calculated from high dose and high dose rate studies for practical application in radiological protection. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in its 2000 report reviewed criteria for setting upper limits of low dose and low dose rate for assessing risks of cancer induction in humans. The criteria suggest that a low dose could be taken to be about 200 mGy and a low dose rate to be about 0.1 mGy per minute (UNSCEAR, 2000, page 79). The value adopted for this reduction factor differs between various organisations. The ICRP in Publication 60 (ICRP, 1991) adopted a DDREF of two and adopted the same value in its 2007 recommendations (ICRP, 2007). The concept of the DDREF has been developed by the ICRP for general application in assessing risks and setting standards in relation to occupational and public exposure to ionising radiation. In the case of medical exposures, differences in dose rate are not so well defined since many protracted medical exposures will occur as a result of giving treatment in fractions.

Since in such circumstances each fraction would generally be delivered at a high dose rate, the DDREF would not necessarily apply and its use is inappropriate. The criteria relating to use of the DDREF and various values that have been suggested are discussed at length elsewhere (UNSCEAR, 2008).

Although radiation exposure can increase the incidence of cancer in exposed populations, there is at present no way of distinguishing the cases caused by radiation exposure from those resulting from other causes. The identification of radiation-induced cancers in a population can therefore only be determined by comparing populations with different exposures. Brenner et al (2003) considered radiation exposures at which a statistically significant increase in cancer risk could be observed. The review of epidemiological data suggested that the lowest dose at which good evidence of an increased risk could be obtained was around 10–50 mSv for a single acute exposure and around 50–100 mSv for a protracted (chronic) exposure.

In analysing data on cancers in populations exposed to high doses, empirically based models have generally been used to describe the variation in radiation-induced risks with time since exposure and across populations. In particular, simple relative (multiplicative) and absolute (additive) risk models have commonly been used for solid cancers. Under these models the relative risk or the annual absolute excess risk, respectively, is assumed to be constant over time and/or populations, over the period of ten or more years following exposure in the case of most solid cancers. For both models, the relative or the absolute excess risk may vary additionally by sex and age at exposure, as indicated above. Since the baseline rates for solid cancers increase rapidly with age, the assumption of constant relative risks over time yields a higher estimate of lifetime risk than does the corresponding absolute risk model. More general models have also been utilised, such as a hybrid model that reduces to either the simple relative or absolute risk model as special cases. Furthermore, models under which the relative risk varies with time since exposure have also been developed.

Analyses of data for the atomic bomb survivors in Japan (Preston et al, 2003) and of some groups of patients given radiotherapy have found raised risks of mortality from non-cancer diseases, particularly circulatory diseases. However, it is not clear whether these risks persist down to low doses (McGale and Darby, 2005; UNSCEAR, 2008). A recent AGIR report examines the risk of circulatory disease after radiation exposure (AGIR, 2010). UNSCEAR (2001) has reviewed information linking various categories of genetic disease to radiation exposure; estimates of these risks are particularly uncertain.

1.3 Background to and Structure of the Current Report

Since the mid-1950s a series of reports from national and international bodies have reviewed information on the induction of cancer by ionising radiation. The main international body working in this area is UNSCEAR which has published a series of reviews of the available data since its first report (UNSCEAR, 1958).

In 1988, the then National Radiological Protection Board (NRPB) reviewed the information available from epidemiological studies and gave estimates of the risk of both radiation-induced leukaemia and solid cancers in the UK population (Stather et al, 1988). Much of the information in the report was drawn from a report by UNSCEAR (1988) which had developed risk estimates based predominantly on the follow-up to

1985 of the atomic bomb survivors in Japan (Shimizu et al, 1988) and the then revised dosimetry system, DS86. The risk of death from radiation-induced solid cancer was calculated for the UK population to be about 12% Sv^{-1} for exposures at high dose rates. This implies that among 100 people each exposed to a radiation dose of 1 Sv, a total of 12 will develop fatal radiation-induced cancer.

It has been found in a number of animal studies that reducing the dose rate results in a reduction in the risk of cancer. This is presumed to be due to repair processes operating in the body (UNSCEAR, 1993). Applying a reduction factor of three to assess the risk of fatal cancer at low dose rates (two for breast) gave a risk of about 4% Sv^{-1}. For a population of working age the risk was calculated to be 8.7% Sv^{-1} at high dose rates and about 3% Sv^{-1} at low dose rates. The choice of reduction factor in the UNSCEAR 1988 report was based principally on the results of animal studies in which the risk of radiation-induced cancer at high and low dose rates could be compared.

Following publication by the NRPB of the report by Stather et al (1988), more information on the follow-up of the Japanese atomic bomb survivors was released by the Radiation Effects Research Foundation (RERF) in Hiroshima. The US Committee on the Biological Effects of Ionizing Radiation of the US National Academy of Sciences had examined the implications of using various dose–response models for calculating lifetime cancer risks after radiation exposure (BEIR V Committee, 1990). The 1990 recommendations of the ICRP had also been published (ICRP, 1991), as well as the first analysis of the UK National Registry for Radiation Workers (NRRW) (Kendall et al, 1992). As a consequence of these developments, the NRPB gave further advice on the risk of radiation-induced cancer for the UK population (NRPB, 1993). The risk of death from radiation-induced solid cancer for the whole population, following exposure at low dose rates, was calculated to be 5.3% Sv^{-1}. This increase in risk, compared to that given in the 1988 report, was primarily due to the adoption of a reduction factor of two when extrapolating findings from acute high doses to low doses and low dose rates, as had been used by the ICRP (1991). For a population of working age the risk of radiation-induced solid cancer mortality was calculated to be 4.5% Sv^{-1}.

Subsequent to the publication of the 1993 NRPB report, further findings have become available from the extended follow-up of the atomic bomb survivors in Japan. These data cover not only cancer mortality (Pierce et al, 1996; Preston et al, 2003), which formed the basis of previous analyses, but also the incidence of cancer at various sites (Preston et al, 2007). In addition, some findings based on further improvements to dose estimates for the survivors have been published (Preston et al, 2004, 2007). Various other studies of radiation and cancer risk have appeared since 1993, including the second and third analyses of the NRRW (Muirhead et al, 1999, 2009) and a pooling of studies of radiation workers in 15 countries (Cardis et al, 2005, 2007). Analyses published up until the end of the 1990s were considered by UNSCEAR in its 2000 report and an updated review of radiation epidemiology – prepared in 2006 – was published in 2008 (UNSCEAR, 2008). Both the new UNSCEAR report and a report by the US BEIR VII Committee (2006) use recently published updated cancer incidence data for the atomic bomb survivors in Japan, in order to model risks of radiation-induced cancer.

In the 2003 AGIR report entitled *Risk of Leukaemia and Related Malignancies following Radiation Exposure*, the principal factors that are known to influence the incidence of leukaemia (including subtypes of the disease) and lymphomas in the population were examined and the evidence linking these malignancies to

radiation exposure was quantified. In addition, the probability of developing leukaemia following radiation exposure was estimated for the UK population (AGIR, 2003).

With the publication of additional data on the risk of radiation-induced solid cancers in a number of epidemiological studies, it is now appropriate to update the previous advice on risks of solid cancers for the UK population. The UK-specific risk estimates for radiation-induced cancer given in this document are not intended to replace the more general values that the ICRP has developed for setting standards in radiological protection for a world population. In that case it is necessary to have values that different countries can use consistently. The UK-specific values are intended for use in calculating late health effects within the UK population where more precise information is required – for example, in accident consequence assessments or in determining probability of causation following significant radiation exposures. They might also be used in examining the effect of medical exposures, particularly when considering the role of age at exposure and differences in the risk of exposure between different organs or tissues.

Chapter 2 of this report describes relevant epidemiological studies of radiation risk and methodological considerations. It addresses the difficulties in assessing lifetime cancer risks when exposed populations have been followed for only a limited period of their total lifespan and also the difficulties involved when estimating risks for the UK population based on studies of other population groups around the world.

The results of various epidemiological studies are reviewed in Chapter 3. These include, in particular, the extended follow-up of the atomic bomb survivors in Japan but also other studies related to people exposed either occupationally, environmentally, or for medical reasons. Information is provided on cancers of:

Oral cavity	Breast (females)
Oesophagus	Uterine cervix
Stomach	Body of uterus
Colon	Ovary
Rectum	Prostate
Liver	Testis
Pancreas	Bladder
Trachea, bronchus and lung	Kidney
Bone and connective tissue	Brain and other central nervous system
Melanoma of skin	Thyroid
Non-melanoma skin	All solid cancers combined

Whilst the above list covers most solid cancers, some forms of the disease are not included owing to a lack of relevant data. Consequently, the risk of all radiation-induced solid cancers combined is also reviewed.

To the extent possible, the information on radiation-induced cancer risk in various organs and tissues is used to develop quantitative information on cancer risks.

The calculated risk of radiation-induced solid cancers for the UK population for both the population as a whole and the working population is presented in Chapter 4, based on models for risk derived from an analysis of epidemiological data. Information is provided on the lifetime risk of incidence and mortality for various ages at exposure. To illustrate the application of these risk models, cancer risks associated with several medical radiation procedures are also presented in Chapter 4.

Chapter 5 gives the summary and conclusions of the report. A glossary is provided and details of the calculation of radiation risks are given in the appendices.

2 Relevant Epidemiological Studies of Radiation Risk and Methodological Considerations

Various epidemiological studies of groups exposed to ionising radiation have examined the subsequent risk of solid cancers. However, some studies are more informative than others. This chapter begins by reviewing some of the key aspects of the design and conduct of epidemiological studies that may be used to estimate the risk of cancer. A list of studies that are relevant to the assessment of solid cancer risks following radiation exposure will then be presented, together with an evaluation of the strengths and limitations of these studies. The aim of the assessments is first to identify whether radiation exposure is a cause of specific cancers and, if so, to use the best available evidence to quantify the dose–response relationships, so that it is possible to obtain an estimate of the magnitude of the risk arising from a given radiation dose.

Epidemiological studies often cannot be used to determine risks associated with specific radionuclides, or with low dose rate exposure. In order to do this, risks must be estimated indirectly, most often with information from *in vivo* studies, which is then combined with the appropriate high dose rate data, often in relation to X- or gamma-ray exposure, such as those from the Japanese atomic bomb survivor Life Span Study (LSS) cohort (Preston et al, 2003, 2004). For example, there is little epidemiological data associated with risks from exposure to tritium, so a recent AGIR subgroup report estimated the likely associated risk by evaluating the relative biological effectiveness (RBE) of this internal emitter relative to gamma radiation and X-rays from the available experimental *in vivo* and *in vitro* data (AGIR, 2007; Little and Lambert, 2008; Little and Wakeford, 2008). Most of the available information on the RBE for this and other types of radiation is derived from experimental *in vivo* and *in vitro* data (NCRP, 1990). Similarly, information on low dose rate risks is often obtained indirectly from epidemiological data derived at high dose rates, such as data from the Life Span Study. Low dose rate risks are derived from these by applying dose and dose rate effectiveness factors, often obtained experimentally (NCRP, 1980). Animal data have occasionally been used to estimate risks to human populations (Carnes et al, 2003).

2.1 Features of Epidemiological Studies

Several different types of epidemiological study can be used to investigate radiation effects. In a *cohort study*, a defined population (preferably with persons exposed to a wide range of doses) is followed forward in time to examine the occurrence of effects (Breslow and Day, 1987). Such a study may be performed by following a current cohort into the future or historically, by constructing a cohort of persons alive at some time in the past and following it forward, possibly to the present. In a *case–control study*,

persons with and without a specified disease (the cases and controls, respectively) are compared to examine differences in exposures. A nested case–control study design, in which cases and controls are selected from a cohort of individuals, can be used when it is difficult to obtain estimates of radiation dose or other exposures for all members of the cohort, but where such data can be collected for a smaller number of persons (Breslow and Day, 1980). For example, in an international study of patients treated for cervical cancer, radiation doses were estimated for patients with various types of second cancer as well as for matched control patients (Boice et al, 1988).

In assessing studies, it is necessary to consider to what extent the findings might be subject to bias (systematic error) or to confounding (ie where another factor explains, entirely or in part, an observed association between the factor and disease under study because of its association with both the study factor and the disease). Cohort studies – particularly those performed prospectively – tend to be less susceptible to biases than case–control studies, which depend on the retrospective collection of data (Boice, 1997). Provided that the potential for biases associated with retrospective data collection – as illustrated below – is minimised, case–control studies can be informative about risks and tend to be more economical than cohort studies, particularly when investigating a rare disease and when attempting to obtain detailed information on potential confounding factors, such as smoking histories in studies of lung cancer among people exposed to elevated levels of radon in homes (Darby et al, 2005a).

In cohort studies it is important to minimise the potential for differences in the degree of follow-up between groups with different exposures, since this can introduce ascertainment bias. For example, Donaldson and Hancock (1996) pointed out that in hospital-based follow-up studies of patients treated for a first cancer, those patients who develop a second cancer would be more likely to return to the hospital or clinic than patients who do not develop a second cancer. If the end of follow-up is taken as the date last seen at the hospital, then many of the disease-free patients may be withdrawn from the study at an early time even though, had they later developed the disease, the follow-up would have been longer. Thus, hospital-based studies are susceptible to the possibility of differential follow-up, which may lead to an overestimation of disease rates.

Ascertainment bias might also arise when studying diseases that are not immediately apparent, such as thyroid tumours without apparent symptoms. Increased levels of screening in a radiation-exposed population may show a raised disease incidence relative to an unscreened group. Ideally, comparisons would be made between groups with a similar level of screening, as, for example, in a study of irradiation for lymphoid hyperplasia in which both the exposed and comparison groups were screened (Pottern et al, 1990). However, if – among those exposed – the level of screening were correlated with dose, then examination of any dose–response relationship would be biased.

In case–control studies, to avoid selection bias it is important that the cases and controls should be chosen from the same defined population and that the ascertainment of cases and controls should be high and subject to the same influences. When it is necessary to approach potential study subjects or their next-of-kin for interviews, the refusal rate should be low for both cases and controls if selection bias is to be avoided. In case–control and some cohort studies where exposures, both to radiation and to other agents, are ascertained retrospectively, it is sometimes necessary to rely upon the study subjects themselves or surrogates (eg relatives) for such information. This might lead to bias if the ability to assess

exposures accurately depends on whether the disease in question arose or not. For example, in a study of naval shipyard workers in the USA, an increased risk of cancer and leukaemia relative to other causes of death was reported among nuclear workers (Najarian and Colton, 1978), when based on radiation-exposure histories ascertained by newspaper reporters from the next-of-kin of deceased workers. However, the findings were not borne out in a subsequent cohort study in which radiation exposures were determined using employment records (Rinsky et al, 1981). In particular, the relatives of workers who died from cancer were more likely to have been located and interviewed than the relatives of other deceased workers. This, in combination with the lower all-cause mortality among nuclear workers relative to the comparison group, contributed to the spurious findings. More generally, the use of historical records, where available, is to be preferred to avoid differential ascertainment of exposures.

Random errors in individual dose estimates tend to conceal genuine differences in cohort studies (Armstrong, 1990), so-called regression dilution. Statistical methods have been developed to adjust risk estimates for such random errors, based on estimates of the magnitude of the errors. These methods have been applied to several radiation-exposed groups, such as the survivors of the atomic bombings in Japan (Pierce et al, 1992) – including the latest analysis of mortality in this study (Preston et al, 2003) – and persons exposed to elevated levels of radon in homes (Darby et al, 2005a, 2006). Whilst it is possible to adjust risk estimates appropriately, random errors also reduce the statistical precision of analyses.

An important facet of any epidemiological study is its statistical power, ie the probability that it will detect a given level of raised risk with a specific degree of confidence. The power of a cohort study will depend on the size of the cohort, the length of follow-up, the baseline rates for the disease under investigation, and the distribution of doses within the cohort, as well as the predicted level of raised risk; increasing any of these will tend to increase statistical power. Similar factors influence the power of case–control studies. Statistical power is generally evaluated before a study is conducted. Afterwards it is more correct to refer to statistical precision, which is reflected in the width of the confidence intervals.

Low statistical power can affect not only estimation of how a particular type of exposure (eg to radiation) influences disease risk but also estimation of how the effect of this exposure may be modified by other factors – for example, of how radiation-induced cancer risks might vary according to the age at which the person is exposed or, say, according to whether the person smokes. Another example concerns the risk of second cancer among patients treated for a first cancer using both radiotherapy and chemotherapy. In order to evaluate the combined effect of different factors on disease risk, it is important as far as possible to measure these factors as precisely and accurately as possible. In particular, as mentioned earlier, random errors in exposure assessment can reduce the statistical precision of analyses. Furthermore, it will tend to be easier to study the combined effect of different factors if each of them individually is a strong risk factor for the disease in question.

Consistency of findings is valuable. If the evidence arises from different types of study, then this indicates that the findings cannot be attributed to problems with a particular study design. In some instances, meta-analyses have been conducted using published data – for example, by Lubin and Boice (1997) and by Pavia et al (2003) in the case of residential radon exposure and lung cancer. However, where possible,

it is better to draw together data at the individual level from the relevant studies. Such combined analyses can be valuable in examining to what extent data on individual confounding factors might affect assessments of differences in the size of the effect across studies and of how risks might be modified by factors such as age and sex. For example, whereas the meta-analysis of Pavia et al (2003) indicated heterogeneity across studies in the relationship between residential radon and lung cancer, this was not the case in the combined analysis by Darby et al (2005a, 2006) that used individual-level data from many of these studies. Such combined analyses also have greater statistical power than is available from the component studies.

In contrast to cohort and case–control studies, which use data on specific individuals, *correlation studies* (sometimes referred to as *ecological studies*) are based on data averaged over groups. A particular form of this study is the geographical correlation study, in which disease rates in geographical areas are compared with average levels of exposures, eg to natural or environmental radiation. Correlation studies are particularly prone to bias (Greenland and Robins, 1994). A notable example concerns exposure to radon in homes and the risk of lung cancer. Using data collected at the level of US counties, Cohen (1997) reported a strong negative correlation between average lung cancer rates and average radon levels, even after adjusting for county-averaged smoking data. However, analyses of case–control data have shown a negative correlation between smoking and radon at the individual level (Lagarde and Pershagen, 1999; Darby et al, 2005a). Adjusting for smoking using individual level data shows an increasing, rather than a decreasing, trend in lung cancer risk with radon in homes (Lubin et al, 2004a; Darby et al, 2005a; Krewski et al, 2005); see also Section 3.9. Thus, while correlation studies can sometimes be useful in generating hypotheses or as a means of detecting large effects, such as the raised risk of thyroid cancer in young people in parts of the former Soviet Union affected by the Chernobyl accident (Kazakov et al, 1992), the potential biases particular to this form of investigation should be borne in mind.

Another type of study is the *randomised controlled trial*, in which persons are randomised to treatment and control groups in a clinical setting. For example, such a trial might compare the effectiveness of, say, radiotherapy and chemotherapy in treating a particular form of cancer. Because of the experimental method employed, such trials are less susceptible to bias and have fewer methodological limitations than either cohort or case–control studies. However, bias might arise if the ascertainment of health outcome were correlated with exposure – for example, if patients given radiotherapy were followed with more (or less) care than patients who received another type of therapy. In addition, restrictions on the eligibility of persons to enter such trials can affect the degree to which the results can be generalised. In practice, only a few randomised trials of the effects of radiotherapy in treating cancer have provided information on radiation risks – for example, an analysis of second cancers (including solid cancers) based on randomised trials of treatments for Hodgkin lymphoma (Franklin et al, 2006).

Cohort and case–control studies generally form the main bases for estimating radiation risks in humans.

2.2 Assessment of Available Studies

Tables 2.1 and 2.3* list cohort and case–control studies of solid cancer risk in groups exposed to ionising radiation, for which an assessment was made of the magnitude of individual exposures and for which the numbers of solid cancers were more than about ten. For ease of presentation, Table 2.1 covers studies of external exposures, mainly to X-rays or gamma radiation, whilst Table 2.3 covers studies of internal exposures from radionuclides taken into the body, normally by inhalation or ingestion. However, in some instances (eg with fallout from the Chernobyl accident), both external and internal exposures were received. These studies were identified through reference to the UNSCEAR (2000, 2008) reports and by Medline searches. Tables 2.2 and 2.4 describe the key strengths and limitations of these studies. Other, less informative studies are listed in an annex to this chapter. These studies generally comprise subgroups of populations included in Tables 2.1–2.4, such as radiation workers who have been included both in studies of specific workforces and in larger combined analyses, or involve small numbers of cancer cases.

Many studies have been conducted – mainly of patients given radiotherapy – which have compared a group of persons exposed to radiation with an unexposed group. Studies of this type that do not contain information on radiation doses cannot be used to quantify the magnitude of radiation-associated risks. Consequently, Tables 2.1–2.4 include only those studies for which radiation exposures have been assessed. However, for certain cancer sites where studies with dosimetry are lacking, reference is made in Chapter 3 to some studies that simply involve comparison of exposed and unexposed groups.

The Life Span Study of the Japanese atomic bomb survivors has a number of advantages over many of the other studies in Table 2.2. In particular, whereas other studies often cover a limited age range and/or a single sex, the Life Span Study covers a large population of all ages and both sexes and hence can be used to derive risks for a whole population. Furthermore, while other studies involve persons who were selected for inclusion, either through a medical condition or by employment in certain occupations, those exposed to radiation from the atomic bombings in Japan were not selected in this way. In particular, the Life Span Study population was identified from a 1950 census of the affected cities, and has been followed up subsequently using a system that provides complete information on deaths occurring throughout Japan. It has been suggested that, because the Life Span Study did not start until five years after the bombings of Hiroshima and Nagasaki, harsh living conditions and malnutrition may have led to selective mortality in the intervening period, with only the healthier members of the population surviving until the start of the study (Stewart and Kneale, 2000). However, analyses of this topic by Little (2002) and Hunter et al (2006) indicate that the associated impact on estimates of radiation-induced cancer risks is unlikely to be large.

The Life Span Study also has the advantage that the range of doses is wide, from several gray down to background dose levels. Indeed, the majority of survivors with a non-zero dose due to the bombings received less than 0.2 Gy (Preston et al, 2003, 2004). Although much of the statistical power of the study

* Tables 2.1–2.4 on the main epidemiological studies on solid cancer risks are given on pp 24–71 of this report. An annex to the chapter then follow, providing details of other, less informative studies (pp 73–90).

arises from those survivors with higher doses, the range of doses encountered allows examination of the dose–response relationship from high values down to low doses. This contrasts with many of the medical studies – where doses amongst those exposed are sometimes not less than several gray – and occupational studies in which only low doses arise in general. Furthermore, the whole-body exposure received by the Japanese atomic bomb survivors differs from the experience of many of those with medical exposures in which only part of the body was irradiated. Ideally, dose estimation in the latter instance would involve calculations for the relevant organs or tissue, so as to allow examination of how radiation affects the risk of cancer for the corresponding sites. Detailed dose estimation of this type has been undertaken in many studies of groups with medical exposures, but not in all of them. The types of models that have been used to describe how radiation-induced cancer risks vary according to dose are described below (page 21) and in Appendix B.

Estimates of doses for the Japanese atomic bomb survivors and for many other radiation-exposed groups are likely to include random errors. Adjustments for such errors have been employed in recent analyses of the Life Span Study (eg Preston et al, 2003) and in a few other analyses, eg of residential radon exposure and lung cancer (Darby et al, 2005a). However, many analyses – whilst recognising that such errors might be present – have not incorporated formal adjustments, often because of difficulties in quantifying the form and structure of such errors. The potential for systematic errors in doses also needs to be borne in mind. For example, there had been concern for some years that neutron doses for the atomic bomb survivors in Hiroshima had been underestimated in the dosimetry system, referred to as DS86, which was introduced in the 1980s (Straume et al, 1992). However, a recent analysis based on a new dosimetry system, entitled DS02, found that changes in neutron dose estimates had little effect on cancer mortality risk estimates for the Japanese atomic bomb survivors (Preston et al, 2004). Further aspects concerning the assessment of doses in epidemiological studies and the impact of uncertainties in dose estimates are described by the US National Cancer Institute (NCI, 1999) and UNSCEAR (2000).

Some of the studies listed in Tables 2.1 and 2.3 involve only mortality data and others involve solely data on cancer incidence. The Life Span Study is one of the few studies to have both types of data. Causes of death listed on death certificates are not always accurate, although this would lead to particular concern only if the recording of cause of death were correlated with the level of exposure. Autopsies were performed on about 14% of the deaths in the Life Span Study cohort during 1950–87, with emphasis being placed over much of this period in autopsying a representative sample of deaths (Ron et al, 1994). It was found that almost 25% of cancers identified at autopsy in this study were not recorded on death certificates. In contrast, analyses of cancer incidence data enable detailed examination of disease subtypes, based upon more accurate diagnoses than are available for mortality data. However, at least in the case of the Life Span Study, mortality data are of value since they provide essentially complete coverage across Japan, whereas the incidence data are restricted to cases diagnosed in and around Hiroshima and Nagasaki and allowance has had to be made for the effects of migration from the two cities (Thompson et al, 1994; Preston et al, 2007). Consequently, the incidence and mortality data for the Life Span Study provide complementary information for risk assessment. Similarly, in other studies incidence data either are not available or may be incomplete. In such instances, mortality data should be of value.

Few studies have followed radiation-exposed groups over their full lifetime. For example, whereas virtually all of the atomic bomb survivors in Japan who were aged 40 years or more at the time of the bombings have since died, more than 80% of those exposed at ages less than 20 years were still alive at the end of the most recent follow-up in 1998 (Preston et al, 2007). Therefore, in trying to assess the lifetime risk of solid cancers associated with radiation exposure, it is valuable to examine how risks varied during the period that has been studied, in order to make projections beyond that time. To this end, the Life Span Study is particularly informative due to its long follow-up: more than 50 years following exposure for cancer incidence (Preston et al, 2007) and mortality (Preston et al, 2003, 2004), as are some of the studies of medically exposed groups, eg patients treated for ankylosing spondylitis (Weiss et al, 1994) or who received multiple chest fluoroscopies (Boice et al, 1991). This topic has been addressed in some combined analyses – for example, of female breast cancer in the Life Span Study and several medically exposed groups (Preston et al, 2002a).

Studies other than the Life Span Study that are listed in Table 2.1 provide information on specific age groups – for example, studies of occupationally exposed groups and of groups exposed in childhood or *in utero*. In particular, information on childhood cancer risks from irradiation *in utero* comes largely from studies of the effects of prenatal X-raying of the abdomen, such as the Oxford Survey of Childhood Cancers (Stewart et al, 1958; Bithell and Stewart, 1975). However, because these studies largely have a case–control design and are restricted to childhood cancer, the Japanese atomic bomb data form the main source of information on cancer risks in adulthood following *in utero* irradiation (Delongchamp et al, 1997; Preston et al, 2008). Combined analyses have been helpful in delineating the effect of age at exposure – for example, in highlighting differences in thyroid cancer risk between exposure early in life and later in childhood (Ron et al, 1995). Since most of the uncertainty in estimating lifetime cancer risks from radiation exposure relates to those exposed at young ages, obtaining a better idea of the role of age at exposure is important for the purposes of risk estimation. Similarly, whilst the inclusion in the Life Span Study of roughly comparable numbers of males and females assists in looking for any differences in risks between sexes, various other studies can contribute to this topic.

Risk associated with an exposure can be expressed as a relative risk, ie incidence among exposed divided by incidence among unexposed, or as an excess absolute risk, ie incidence among exposed minus incidence among unexposed. An excess absolute risk can be estimated directly in a cohort study but only indirectly in a case–control study. A relative risk estimate from a case–control study can be used to estimate the excess absolute risk if the incidence in unexposed subjects is known since the relative risk equals one plus the excess relative risk and the excess absolute risk equals the excess relative risk multiplied by the incidence in the unexposed. However, this estimation assumes that the combined risk attributable to the exposure of interest and to other factors is the product of these components, ie corresponding to a multiplicative model. This approach would not be feasible if the combined risk were the sum of these components, ie corresponding to an additive model.

Many epidemiological studies of radiation and solid cancer risk have been performed in countries other than the UK. If the underlying solid cancer rates (Parkin et al, 2005) in these countries differ greatly from those of the UK, then the format of the model used to transfer the risks between the populations can have a significant effect on the risk estimates. Figure 2.1 illustrates the problem. If an additive model is used to transfer risk between the Life Span Study population and the UK population, then any differences

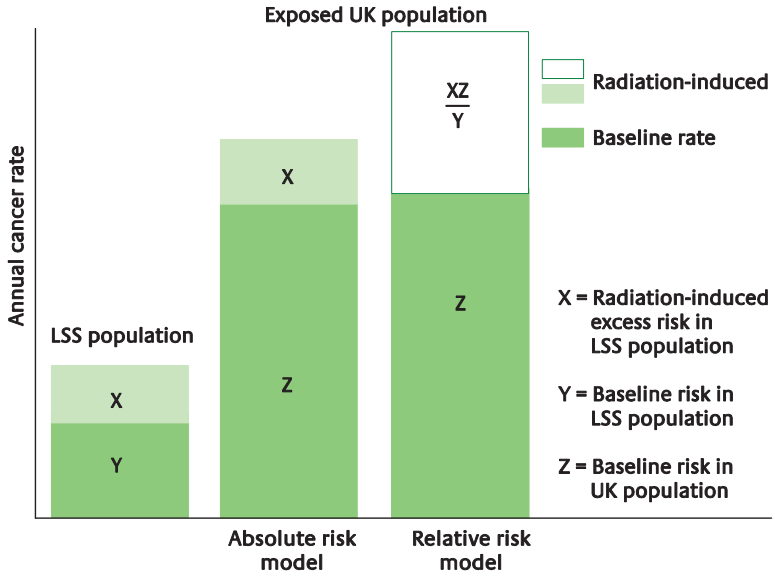


FIGURE 2.1 Effect on predicted risk of transferring risk between populations with differing baseline rates using the absolute and relative risk models (where LSS = Life Span Study)

in the baseline cancer rates do not affect the absolute size of the excess risk. If a relative risk model is used, then the absolute size of the excess risk will vary in proportion to the relative sizes of the baseline risks in the two populations. Thus, it is necessary, when estimating radiation risks for the UK population, to consider whether – for a particular type of cancer – the multiplicative or the additive model is more appropriate. A complicating factor is that, for some cancers, baseline rates have varied over time. For example, in Japan, the incidence of lung and breast cancer has been increasing in recent decades, whereas stomach cancer rates have been falling.

One way of addressing this issue involves examining whether – for a given level of radiation dose – either the relative risk or the excess absolute risk is consistent across studies of irradiated populations with differing baseline rates. Ideally this would be carried out through a formal combined analysis of data from different cohort studies, such as the breast cancer analysis by Preston et al (2002a) that was based on the Life Span Study and several studies of medically exposed groups; see Chapter 3 for further details. Since there are few formal analyses of this type, Chapter 3 also includes some informal comparisons of relative and absolute risks, although it should be borne in mind that other factors may affect such between-study comparisons. Another approach is to consider how factors that are known to explain much of the difference in baseline rates between populations modify radiation risk, using those studies where detailed information on both radiation and such factors has been collected. For example, in the case of lung cancer, studies with individual data on smoking as well as radiation may be particularly informative; these are considered in Chapter 3. The findings from consideration of this topic – made on a site-by-site basis and considering uncertainties – are used when developing risk estimates for the UK population in Chapter 4.

The most widely accepted model used to define the relationship between risk and exposure is a linear function. This model has formed the basis of solid cancer risk estimation for many years, as it has been found to provide a good fit in many studies including the Life Span Study, medical studies and worker studies. Other proposed functions include linear-threshold (where the linear relationship begins only once a certain dose threshold is exceeded) and linear–quadratic models. Many studies lack the statistical power necessary to explicitly reject a linear model in favour of these alternative models.

Whilst the Life Span Study is particularly informative about the effects of a single acute exposure, it does not provide direct information on the effects of multiple or protracted exposures. Some studies of medically exposed groups involve multiple exposures, given as therapy for cancer or non-malignant disease. However, the doses in each of these exposures are often high. In contrast, doses received by radiation workers are generally low and protracted. A difficulty with many studies of this type is their low statistical power, owing to the low doses received and often a small study size. However, it is possible to obtain greater statistical power from large studies of radiation workers (eg Muirhead et al, 2009) or by performing combined analyses of such studies (eg Cardis et al, 1995, 2005b).

Low statistical power can also affect analyses of cancer risks at low radiation doses. This problem is particularly acute for rarer cancers, where – even in large studies such as the Life Span Study – the numbers of cases or deaths at low doses may be limited. In these instances, the failure to find a statistically significantly raised risk at low doses does not by itself mean that there is no raised risk at these levels; rather, the data are insufficient to distinguish between a dose threshold for risk and a relatively small raised risk. Tabulated below are the sample sizes needed to detect certain levels of risk, assuming a linear dose–response relationship and the dose distribution of the Life Span Study participants (eg approximately 0.1 Sv for both colon and bone marrow); these were derived from UNSCEAR (2008). The excess relative risk (ERR) value of 4 represents the level of risk observed for leukaemia mortality in the Life Span Study, while the 0.4 level is similar to that observed for all solid cancers.

Level of ERR Sv^{-1} desired to detect	Statistical power desired	Minimum number of cases for statistical significance (1-sided, p = 0.05)
4.0	80%	34
0.4	80%	765
0.04	80%	50,000

It should also be noted that if the assumed dose–response relationship is linear–quadratic rather than linear (as found for leukaemia risk) then the number of cases will be even larger.

Another factor to consider in low dose studies is the relationship between the number of cases needed to detect a particular level of risk and the average dose of the exposed group. The table below examines this relationship, again assuming a linear dose–response relationship. The 0.1 Sv average doses here are similar to the Life Span Study average colon and bone marrow doses.

Level of ERR Sv^{-1} desired to detect	Average dose (Sv)	Statistical power desired	Minimum number of cases for statistical significance (1-sided, p = 0.05)
4.0	1.0	80%	9
0.4	1.0	80%	37
4.0	0.1	80%	43
0.4	0.1	80%	700
4.0	0.01	80%	910
0.4	0.01	80%	45,700

The studies in Tables 2.1 and 2.2 generally relate to external exposures to gamma radiation or X-rays. These are classified as low linear energy transfer (LET) radiations, because they lose little energy along their path. In contrast, high linear energy transfer radiations such as neutrons lose energy much more densely along their paths and – for a given level of absorbed dose – would be more damaging. There have been few epidemiological studies of populations exposed to neutrons. Neutrons form a small component of the doses received by the Japanese atomic bomb survivors, but it is not possible to estimate risks specific to neutron exposures in this population. More information has arisen in recent years from studies of aircrew exposed to external radiation of varying energies that cover both high and low LET radiations. Many of these studies have been limited by small numbers of cancer cases and deaths and the absence of individual measures of radiation exposure and data on potential confounding factors. Some of these issues have been addressed by combined analyses, eg of European cohorts of aircrew (Langner et al, 2004; Zeeb et al, 2003), and by attempting to estimate radiation exposures based on log books and flight records. Even in these larger studies, statistical power and possible confounding are still of concern, because the doses received are generally very low.

Tables 2.3 and 2.4 concern studies of internal radiation exposures. These cover both low LET exposures to beta radiation, eg medical or environmental exposures from radioactive iodine, and high LET exposures to alpha radiation, eg from radon, radium or plutonium. Overall, there are fewer epidemiological data available on cancer risks from such exposures than on those from external exposures (CERRIE, 2004). The characterisation of organ doses is often difficult and in many instances has not been performed on an individual basis. Indeed, the non-uniformity and high toxicity of exposures may mean that organ dose is insufficient for risk assessment. In addition, measurements at the time of exposure are sometimes lacking, eg for some of the early uranium miners (Lubin et al, 1995). However, more information has been obtained in recent years, particularly on the effects of radon in the home and occupational exposure to plutonium.

Interpretation of some studies is complicated because the groups concerned have received a mixture of exposures. For example, some of the workers at the Mayak complex in the Southern Urals in Russia (eg radiochemical and plutonium production workers) received both internal and external exposures to high and low LET radiations, as well as possible chemical exposures (Koshurnikova et al, 2002). Radon-exposed miners were sometimes also irradiated externally, as well as having been exposed to carcinogens

other than radiation. Furthermore, in the case of patients who received Thorotrast (an X-ray contrast medium), not only their radiation exposure but also the chemical effect of Thorotrast and perhaps the patients' medical condition might have influenced their subsequent cancer risk (BEIR IV Committee, 1988). Care is needed to distinguish between the effects of these exposures.

2.3 Conclusions

There is a considerable amount of information on the risks of solid cancer from various epidemiological studies of radiation-exposed populations. However, the amount of information from these studies varies considerably, because of differences in, *inter alia*,

a statistical precision, which in itself is influenced by factors such as the numbers of cases or deaths available for study,

b potential for bias (systematic error), which may arise – for example – through the manner in which the study population was identified and in which the cancers were ascertained,

c availability and reliability of individual estimates of radiation dose,

d scope of the study, eg whether it covers only low doses or only high doses, only childhood exposures or only adult exposures, or low or high LET radiations.

Overall, the Life Span Study of Japanese atomic bomb survivors is the single most informative study on the risks of radiation-induced solid cancers. However, some studies of medical, occupational and environmental exposures are also informative when specific cancers and/or specific types of exposure are being considered (eg protracted exposures or high LET radiations). The findings from these studies are described in Chapter 3.

TABLE 2.1 Main epidemiological studies of solid cancers in relation to external radiation exposures (based on UNSCEAR, 2008)

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
LOW LINEAR ENERGY TRANSFER EXPOSURES				
1	**Exposure to atomic bombings**			
1.1	Life Span Study, 1958–98 (Thompson et al, 1994; Preston et al, 2007)[b]	Cohort (incidence)	44,635 exposed persons[c] 60,792 unexposed persons[d] 59% female Age: 0–>90	Japan
1.2	Life Span Study, 1950–87 (Preston et al, 2003)	Cohort (mortality)	49,114 exposed persons 37,458 unexposed persons Age: 0– >90	Japan
2	**Treatment of malignant disease**			
2.1	**Childhood exposures only**			
2.1.1	International childhood cancers (Tucker et al, 1987, 1991)	Case–control (incidence) within a 9,170-member cohort	112 exposed persons 388 unexposed persons 45% female Age: 0–18 (mean 7)	Canada, France, Netherlands, Italy, UK, USA
2.1.2	Bone cancer after childhood cancer (Hawkins et al, 1996)	Case–control (incidence) largely within a 13,175-member cohort	208 exposed persons 71 unexposed persons Age: 0–14	UK
2.1.3	Retinoblastoma (Wong et al, 1997; Kleinerman et al, 2005a,b)	Cohort (incidence)	849 exposed persons with hereditary retinoblastoma 114 unexposed persons with hereditary retinoblastoma 638 persons with non-hereditary retinoblastoma 47% female Age: 0–7	USA

Table 2.1 extends on to the facing page and continues for ten pairs of pages

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
13–53	2,764,730 (26.2)	Predominantly gamma radiation from nuclear explosions [e]	Individual estimates based on the DS02 dosimetry system, derived from detailed shielding histories	Oral cavity and pharynx*, salivary gland*, oesophagus, stomach*, colon*, rectum, liver*, gallbladder, pancreas, lung*, non-melanoma skin*, breast*, uterine cervix, body of uterus, ovary*, prostate, kidney (renal cell), bladder*, brain and other central nervous system*, thyroid*
5–52	3,062,046 (35.4)	Predominantly gamma radiation from nuclear explosions [e]	Individual estimates based on the DS86 dosimetry system, derived from detailed shielding histories [f]	All solid cancers combined*, oesophagus*, stomach*, colon*, rectum, liver*, gallbladder*, pancreas, lung*, breast (females)*, uterus ovary*, prostate, bladder*, other solid tumours*
5–48	50,609 (5.5)	Adjuvant radiotherapy	Individual doses from therapy records and experimental measurements	Thyroid*, bone sarcoma*
3–>20	n.a.	External radiotherapy	Individual doses from therapy records and experimental measurements	Bone*
1–>60	44,481 (27.8)	External radiotherapy	Individual doses from therapy records and experimental measurements	Buccal cavity*, colon, nasal cavities*, lung, bone*, soft tissue sarcoma*, melanoma of skin, breast (females), body of uterus, bladder, eye and orbit*, brain and other central nervous system*

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
2.1.4	Childhood cancers (de Vathaire et al, 1995, 1999a,b; Little et al, 1998a; Guérin et al, 2003, 2007; Menu-Branthomme et al, 2004: Guibout et al, 2005)	Cohort (incidence)	3,109 exposed persons 1,291 unexposed persons 45% female Age: 0–16 (mean 7)	France, UK
2.1.5	Childhood Hodgkin disease (Bhatia et al, 1996)	Cohort (incidence)	1,380 persons 8% unexposed 35% female Age: 1–16 (median 11)	Canada, France, Italy, Netherlands, UK, USA
2.1.6	Childhood Cancer Survivor Study – thyroid cancer (Sigurdson et al, 2005; Ronckers et al, 2006)	Case–control (incidence) within a cohort of 14,054 five-year survivors	69 cases (63 exposed) 261 controls (197 exposed) 71% female Age: 0–20	Canada, USA
2.1.7	Childhood Cancer Survivor Study – central nervous system tumours (Neglia et al, 2006)	Case–control (incidence) within a cohort of 14,361 five-year survivors	116 cases 464 controls	Canada, USA
2.1.8	Soft tissue sarcoma after childhood cancer (Jenkinson et al, 2007)	Case–control (incidence) largely within a 16,541-member cohort	53 cases (40 known to have been exposed) 179 controls (114 known to have been exposed) Age: 0–14	UK
2.2	**Adult exposures (possibly also including exposures in childhood)**			
2.2.1	Cervical cancer cohort I (Boice et al, 1985)	Cohort (incidence)	82,616 exposed females 99,424 unexposed females Age: <30–>70	Canada, Denmark, Finland, Norway, Slovenia, Sweden, UK, USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
3–48	66,000 (15)	External radiotherapy	Individual doses from therapy records and experimental measurements	All solid cancers combined*, melanoma of skin, breast (females)*, bone*, soft tissue sarcoma*, brain*, thyroid*
0–37 (median 11.4)	15,660 (11.3)	Radiotherapy	Individual doses from therapy records and experimental measurements	Breast (females)*, thyroid*, other solid cancers*
5–>20	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Thyroid*
5–>20	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Glioma*, meningioma*
3–>20 (10)	n.a.	External radiotherapy	Individual doses from therapy records and experimental measurements	Soft tissue sarcoma*
1–>30	1,278,950 (7.0)	Radiotherapy, including external beam and intracavity application	Data on typical range of estimates for specific organs and phantom measurements	Oral cavity, salivary gland, oesophagus*, stomach, small intestine*, colon, rectum*, liver, gallbladder, pancreas*, lung*, breast (females), uterine corpus and ovary, other genital*, kidney, bladder, melanoma of skin, non-melanoma skin, brain, bone, connective tissue, thyroid

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
2.2.2	Cervical cancer cohort II (Kleinerman et al, 1995)	Cohort (incidence)	49,828 exposed females 16,713 unexposed females 19,652 females with missing treatment data Age: <40–>60	Denmark, Finland, Norway, Sweden, USA
2.2.3	Cervical cancer case–control (Boice et al, 1988)	Case–control (incidence)	4,173 cases 6,857 controls Age at treatment: <30–>70	Austria, Canada, Czecho-slovakia, Denmark, Finland, Germany, Iceland, Italy, Norway, Sweden
2.2.4	Lung cancer following breast cancer (Inskip et al, 1994)	Case–control (incidence) within a cohort of 21,106 females	61 cases 120 controls 38 exposed females 143 unexposed females Age: 35–72 (mean 50)	USA
2.2.5	Contralateral breast cancer (Boice et al, 1992)	Case–control (incidence) within a cohort of 41,109 females	655 cases 1,189 controls 449 exposed females 1,395 unexposed females Age at treatment: <45–≥55 (mean 51 at diagnosis)	USA
2.2.6	Contralateral breast cancer (Storm et al, 1992)	Case–control (incidence) within a cohort of 56,540 females	529 cases 529 controls 157 exposed females 901 unexposed females Age at diagnosis: <45–>60 (mean 51 at diagnosis)	Denmark
2.2.7	Soft tissue sarcoma following breast cancer (Karlsson et al, 1998b)	Case–control (incidence) within a cohort of 122,991 females	107 cases 321 controls 310 exposed females 86 unexposed females 32 females with unknown exposure status Age at diagnosis: 29–86 (mean 59 at diagnosis)	Sweden

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
1–>30	897,467 (10.4)	Radiotherapy, including external beam and intracavity application	Data on typical range of estimates for specific organs and phantom measurements	Oesophagus, stomach, small intestine, colon, rectum*, liver, pancreas*, larnyx, lung*, breast (females), uterine corpus*, vagina, vulva, ovary*, kidney, bladder*, bone*, connective tissue, thyroid
1–>30 (7.0 years per case)	n.a.	Radiotherapy, including external beam and intra-cavity application	Individual doses from therapy records	Stomach*, small intestine, colon, rectum*, pancreas, breast (females), body of uterus*, vagina*, ovary, vulva, bladder*, bone*, connective tissue, thyroid
10–46 (18 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung
7–55 (~13 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Contralateral breast among females less than 45 years at exposure*, contralateral breast in older females
12–47 (~16 years per case)	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Contralateral breast (females)
Up to 35 (10 years per case)	n.a.	Radiotherapy	Total absorbed energy from radiotherapy, and location of sacroma in relation to the treatment region	Soft tissue sarcoma

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
2.2.8	Lung cancer following Hodgkin disease (international I) (Kaldor et al, 1992)	Case–control (incidence)	98 cases 259 controls 303 exposed persons 54 unexposed persons 15% female	Canada, Denmark, Finland, France, Norway, Slovenia, UK
2.2.9	Lung cancer following Hodgkin disease (international II) (Travis et al, 2002; Gilbert et al, 2003)	Case–control (incidence) nested within a cohort of 19,046 one-year survivors	227 cases 455 controls Age: <30–>60	Canada, Denmark, Finland, Netherlands, Sweden, USA
2.2.10	Breast cancer following Hodgkin disease (international) (Travis et al, 2003a, 2005a; Hill et al, 2005)	Case–control (incidence) within a cohort of 3,817 female patients	105 cases 266 controls 96 cases (91.4%) and 227 (85.3%) controls treated with radiation (>4 Gy) and/or alkylating agents Age <30 at exposure	Canada, Denmark, Finland, France, Netherlands, Sweden, USA
2.2.11	Breast cancer following Hodgkin disease (Hancock et al, 1993)	Cohort (incidence/ mortality)	855 exposed females 30 unexposed females Age: 4–81 (mean 28)	USA
2.2.12	Thyroid disease following Hodgkin disease (Hancock et al, 1991)	Cohort (incidence)	810 persons treated with radiation alone 920 persons given radiation and chemotherapy 57 patients with chemotherapy alone 41% female Age: 2–82 (mean 28)	USA
3	**Treatment of benign disease**			
3.1	**Exposures to children only** [g]			
3.1.1	New York tinea capitis (Shore et al, 2002, 2003)	Cohort (incidence)	2,224 exposed persons 1,380 unexposed persons 12.8% female Age at treatment: 1–15 (mean 7.8)	USA
3.1.2	Israeli tinea capitis (Ron et al, 1988, 1989, 1991; Sadetzki et al, 2005, 2006) [h]	Cohort (incidence/ mortality)	10,834 exposed persons 16,226 unexposed persons 50% female Age: <1–15 (mean 7.1)	Israel

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
1–>10	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung
1–>20	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung*
7–30 (median 18.0)	n.a.	Radiotherapy	Individual doses from therapy records	Breast (females)
0–29	8,832 (10)	Radiotherapy	Individual doses from therapy records	Breast (females)*
n.a.	n.a. (9.8)	Radiotherapy	Estimated thyroid dose based on treatment records	Thyroid*
10–>50	125,357 (34.8)	X-ray induced epilation	Representative doses based on standard treatment	Salivary gland, lung, melanoma of skin, non-melanoma skin*, breast (females), brain*, thyroid*
26–38	686,210 (25.4)	X-ray induced epilation	Individual doses from phantom measurements based on institution and age	Incidence: thyroid*, skin*, brain*, salivary gland*, breast (females) Mortality: head and neck*

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
3.1.3	Rochester thymic irradiation (Hildreth et al, 1985, 1989; Shore et al, 1993)	Cohort (incidence)	2,652 exposed persons 4,823 unexposed persons 42% female Age: 0–1	USA
3.1.4	Tonsil irradiation (Schneider et al, 1985, 1993, 1998, 2008)	Cohort (incidence)	3,112 exposed persons [i] 39.8% female Age: 0–15 (mean 4.3) [j]	USA
3.1.5	Tonsil, thymus or acne irradiation (DeGroot et al, 1983)	Cohort (incidence)	416 exposed persons Age: mean 7.1	USA
3.1.6	Thymus adenitis screening (Maxon et al, 1980)	Cohort (incidence/ prevalence)	1,266 exposed children 958 unexposed children Age: mean 3.6	USA
3.1.7	Lymphoid hyperplasia screening (Pottern et al, 1990)	Cohort (incidence/ prevalence)	1,195 exposed persons 1,063 unexposed persons 40% female Age: 0–17 (mean 6.9)	USA
3.1.8	Childhood skin haemangioma: Stockholm (Lundell, 1994; Lundell et al, 1994, 1996; Lundell and Holm, 1995; Karlsson et al, 1998a)	Cohort (incidence/ mortality)	14,351 exposed persons 67% female Age: 0–1.5 (mean 0.5)	Sweden
3.1.9	Childhood skin haemangioma, Gothenburg (Lindberg et al, 1995; Karlsson et al, 1998a)	Cohort (incidence)	11,914 exposed persons 88% aged <1 year	Sweden
3.1.10	Childhood skin haemangioma (Dondon et al, 2004)	Cohort (mortality)	4,940 exposed persons 2,097 unexposed persons Age: <15	France

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
23–>50	220,777 (29.5)	X-ray therapy	Individual doses from therapy records	Skin, breast (females)*, thyroid*
0–50	134,734	X-ray therapy	Individual doses from therapy records and phantom measurements	Skin*, thyroid*, benign parathyroid*, salivary gland*, neural tumours*
n.a.	11,000 (26.4)	Radiotherapy	Individual doses from therapy records	Thyroid*
n.a.	n.a.	Radiotherapy	Estimated mean dose to thyroid	Thyroid*
12–44	66,000 (29)	X-ray therapy	Individual doses from therapy records and phantom measurements	Thyroid nodular disease*
1–67	406,355	Radiotherapy	Individual organ doses from therapy records and phantom measurements	Thyroid*, breast (females)*, all other sites
0–69	370,517 (31.1)	Radiotherapy	Individual organ doses from therapy records and phantom measurements	Thyroid*, other endocrine glands*, central nervous system*, all other sites
0–29	137,612 exposed 57,702 unexposed	Radiotherapy	Individual organ doses from therapy records and phantom measurements	All cancers combined

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
3.2	**Exposures to females only**			
3.2.1	Benign gynaecological disease (Inskip et al, 1990)	Cohort (mortality)	4,153 exposed females Age: 13–88 (mean 46.6)	USA
3.2.2	Metropathia haemorrhagica (Darby et al, 1994)	Cohort (mortality)	2,067 exposed females Age: 35–60	UK
3.2.3	New York acute post-partum mastitis (Shore et al, 1986; Shore, 1990)	Cohort (incidence)	571 exposed females 993 unexposed females Age: 14–>40 (mean 27.8)	USA
3.2.4	Benign breast disease (Mattson et al, 1993, 1995, 1997)	Cohort (incidence)	1,216 exposed females 1,874 unexposed females Age: 10–>85	Sweden
3.2.5	Metropathia haemorrhagica (Ryberg et al, 1990)	Cohort (incidence)	788 exposed females 1219 unexposed females	Sweden
3.3	**Exposures to males and females**			
3.3.1	Ankylosing spondylitis (Weiss et al, 1994)	Cohort (mortality)	13,914 exposed persons 16.5% female Age: <20–>60	UK
3.3.2	Peptic ulcer (Griem et al, 1994; Carr et al, 2002)	Cohort (mortality)	1,859 exposed persons 1,860 unexposed persons 19.8% female Age: <35–>55 (mean 49)	USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
0–60	109,910 (26.5)	Intrauterine radium-226	Individual doses from therapy records and phantom measurements	Stomach, colon*, rectum, liver and gallbladder, pancreas, lung, bone, female breast, cervix, all uterus*, other genital sites*, bladder*, kidney, brain and other central nervous system*
5–>30	53,144 (25.7)	X-ray therapy	Individual doses from therapy records and phantom measurements	Colon*, rectum, lung, breast (females), all uterus, cervix, ovary, bladder*
20–35	38,784 (24.8)	X-ray therapy	Individual doses from therapy records	Skin, breast (females)*
5–60	56,900 (18)	X-ray therapy	Individual doses from therapy records and phantom measurements	Stomach*, liver, pancreas, lung, breast (females)*
0–56	9289 irradiated 1219 unirradiated	Intrauterine radium-226 and/or X-ray therapy	Individual doses from therapy records	All sites, brain, thyroid, trachea and bronchus, breast, stomach, colon, rectum, pancreas, ovary, cervix, uterus, kidney, bladder, lymphatic leukaemia
1–57	245,413 (17.6)	X-ray therapy	Individual doses for a 1 in 15 sample of the population	Pharynx, oesophagus*, stomach, colon*, rectum, liver, gallbladder, pancreas*, larynx, lung*, bone*, connective and soft tissue*, skin, breast (females and men), cervix uteri, other uterus, ovary, prostate*, bladder*, kidney*, spinal cord, thyroid, all neoplasms other than leukaemia
2–61	92,979 (25.0)	X-ray therapy	Individual doses from therapy records and experimental measurements	Buccal and pharnyx, oesophagus, stomach*, colon, rectum, liver, pancreas*, larynx, lung*, breast (females), all genital (females), prostate, bladder, kidney, brain, thyroid

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
4	**Diagnostic examinations**			
4.1	Massachusetts TB fluoroscopy – breast cancer incidence study (Shore et al, 1990; Boice et al, 1991)	Cohort (incidence)	2,367 exposed females 2,427 unexposed females Age: 12–50 (mean 26)	USA
4.2	Massachusetts TB fluoroscopy – mortality study (Davis et al, 1989)	Cohort (mortality)	6,285 exposed persons 7,100 unexposed persons 49% female Age: 12–50 (mean 26)	USA
4.3	TB fluoroscopy (Howe, 1995; Howe and McLaughlin, 1996)	Cohort (mortality)	25,007 exposed persons 39,165 unexposed persons 50% female Age: <20–>35 (mean 28)	Canada
4.4	Scoliosis (Doody et al, 2000)	Cohort (mortality)	4,822 exposed females 644 unexposed females Age: 0–19 (mean 10.6)	USA
4.5	Diagnostic X-rays (Inskip et al, 1995)	Case–control (incidence)	484 cases 484 controls 736 exposed persons 232 unexposed persons 77% female Age: <20–>60	Sweden
4.6	Occupational X-rays (Boffetta et al, 2005)	Case–control (incidence)	2,589 cases 2,859 controls	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia
4.7	Medical and dental X-rays (Los Angeles) (Preston-Martin et al, 1988)	Case–control (incidence)	408 cases 408 controls 62% female	USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
0–>50	54,609 (11.4)	Multiple X-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements and computer simulations	Breast (females)*, skin
0–>50	331,206 (24.7)	Multiple X-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements and computer simulations	Breast (females)*, oesophagus*, lung
0–57	1,608,491 (25.1)	Multiple X-ray chest fluoroscopies	Individual exposures from medical records and doses from phantom measurements	Lung, breast (females)*
3–>60	218,976 (40.1)	Diagnostic X-rays	Average dose based on number of treatments and estimated doses from published literature	Breast (females)*
5–>50	n.a.	Diagnostic X-rays	Average dose based on number and type of procedures and estimated doses from published literature	Thyroid
n.a.	n.a.	Diagnostic X-rays	Numbers of occupational X-ray examinations	Lung*
2–64	n.a.	Medical and dental diagnostic X-rays	Average dose based on number and type of procedures and estimated doses from published literature	Parotid gland*

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
4.8	Dental X-rays (Washington state) (Longstreth et al, 2004)	Case–control (incidence)	200 cases 400 controls	USA
5	**Prenatal exposures**			
(Note: A full list of studies of prenatal X-ray exposures is given by Little, 1999; the largest studies are listed here)				
5.1	Oxford Survey of Childhood Cancers (Stewart et al, 1958; Bithell and Stewart, 1975; Knox et al, 1987)	Case–control (mortality)	14,491 cancers 14,491 controls 3,797 exposed persons 25,185 unexposed persons 56% female Exposure *in utero*	UK
5.2	New England childhood cancers (Monson and MacMahon, 1984)	Case–control (mortality)	704 leukaemias 638 other cancers 14,294 controls 1,506 exposed persons 14,130 unexposed persons 49.2% female Exposure *in utero*	USA
5.3	Survivors of atomic bombings (Delongchamp et al, 1997; Preston et al, 2008)[k]	Cohort (incidence/ mortality)	1,078 exposed persons 2,211 unexposed persons 50.7% female Exposure *in utero*	Japan
6	**Occupational exposures**			
6.1	Nuclear workers (Cardis et al, 1995)	Cohort (mortality)	95,673 exposed persons 15% female	Canada, UK, USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
n.a.	n.a.	Dental diagnostic or procedural X-rays	Numbers and types of X-ray examinations	Intracranial meningioma
16 (max)	n.a.	Maternal X-rays during pregnancy	Number of exposures with a model for dose per exposure	All solid tumours (combined)*
20 (max)	n.a.	Maternal X-rays during pregnancy	Number of exposures	All solid tumours combined
5–47	n.a.	Maternal exposure to gamma and neutron radiation at high dose rate	Mother's estimated uterus dose (mainly using DS86)	Cancers of the digestive system*, female-specific cancers*, other solid cancers
Up to 42	2,124,526 (22.2)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All cancers other than leukaemia, buccal and pharynx, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, nasal cavity, larynx, lung, pleura, bone, connective tissue, melanoma of skin, breast (females), cervix uteri, other uterus*, ovary, prostate, testis, bladder, kidney, brain and other central nervous system, thyroid, ill-defined and secondary

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
6.2	Nuclear workers – 15 countries (Cardis et al, 2005b, 2007; Vrijheid et al, 2007)	Cohort (mortality)	407,391 exposed persons 10% female	Australia, Belgium, Canada, Finland, France, Hungary, Japan, South Korea, Lithuania, Slovak Republic, Spain, Sweden, Switzerland, UK, USA
6.3	Nuclear workers (Iwasaki et al, 2003)	Cohort (mortality)	175,939 men	Japan
6.4	National Dose Registry of Canada (Sont et al, 2001)	Cohort (incidence)	191,333 monitored workers 50% female	Canada
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	Cohort (incidence/ mortality)	174,541 monitored workers 10% female	UK
6.6	Portsmouth naval shipyard: lung cancer study (Yiin et al, 2007)	Case–control (mortality) nested within a cohort of 37,853 workers	1,097 cases 3,291 controls	USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 42	5,192,710 (12.7)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All solid cancers (combined)*, buccal and pharynx, oesophagus, stomach, small intestine, colon, rectum, liver, biliary tract, pancreas, nasal cavity, larynx, lung*, pleura, bone, connective tissue, melanoma of skin, breast (females), cervix uteri, other uterus, ovary, prostate, testis, bladder, kidney, brain and other central nervous system, thyroid, ill-defined and secondary
Up to 12	~1,390,000 (7.9)	Exposures in nuclear power plants, fuel processing and research facilities	Recorded exposures to external radiation	Oral and pharynx, oesophagus*, stomach*, colon, rectum*, liver, gallbladder, pancreas, lung, prostate, bladder, kidney and other urinary, brain and other central nervous system
Up to 38	2,667,903 (13.9)	Dental, medical, industrial and nuclear power	Recorded exposures to external radiation	All cancers other than leukaemia (combined)*, colon, rectum, pancreas, larynx, lung, melanoma of skin, prostate, testis, bladder
Up to 55	~3,900,000 [l] (22)	Exposures in nuclear power plants, fuel cycle, defence and weapons production, research and industry	Recorded exposures to external radiation	Mouth, tongue and pharynx, oesophagus, stomach, large intestine, rectum*, liver, gallbladder, pancreas, larnyx, trachea, bronchus and lung, pleura, bone, connective and soft tissue, all skin*, melanoma of the skin, other skin cancers*, breast (females), all uterus, ovary, prostate, testis, bladder, kidney, brain, thyroid, ill-defined and secondary, all cancers other than leukaemia (combined)*
Up to 51	n.a.	Building, overhauling and repairing nuclear submarines	Recorded exposures to external radiation	Lung

The notes to the table are given on p 42

TABLE 2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
6.7	Chernobyl clean-up workers (Rahu et al, 2006)	Cohort (incidence/ mortality)	4,786 males from Estonia 5,546 males from Latvia Age: <30–>60	Estonia, Latvia
6.8	Chernobyl clean-up workers (Ivanov et al, 2002, 2004, 2008, 2009)	Cohort (incidence)	55,718 men Mean age in 1986: 33 75,283 men for thyroid analysis (Ivanov et al, 2008)	Russian Federation
6.9	Mayak workers (Shilnikova et al, 2003)	Cohort (mortality)	21,557 workers (17,157 workers monitored for external radiation) 24% female Mean age at hire: 24.2	Russian Federation
7	**Natural radiation**			
7.1	Yangjiang (Sun et al, 2000; Tao et al, 2000)	Cohort (mortality)	125,079 persons in high background and control areas ~50% female All ages	China

Notes

a An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a statistically significantly higher proportion of the cases were exposed to radiation (case–control studies).
b For some types of cancer, analyses have been conducted using more recent data, as described in Chapter 3.
c Those exposed to more than 0.005 Sv weighted colon dose (ie the sum of the gamma and neutron doses, with the latter multiplied by a factor of 10).
d Includes 25,247 persons not in the relevant city at the time of the bombing.
e There was also a small neutron component to these exposures.
f Preston et al (2004) have reported findings for all solid cancers combined, but not for individual solid cancer sites, based on the new DS02 dosimetry system and three years of further follow-up.
g Some of the other studies listed in Table 2.1 include both children and adults.
h The numbers quoted are based on the analyses by Ron et al (1988, 1989, 1991).
i Figures quoted by Schneider et al (2008).
j Figures quoted by Schneider et al (1993).
k The numbers quoted are based on the analysis by Delongchamp et al (1997).
l Value based on zero lag.

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
0–12	113,194 (11)	Emergency and recovery work in the vicinity of Chernobyl	Recorded radiation doses	Thyroid, brain, all cancers combined
5–15	509,141 (9.1) 1,117,740 for thyroid analysis (Ivanov et al, 2008)	Emergency and recovery work in the vicinity of Chernobyl	Recorded radiation doses	Lip, oral cavity and pharnyx, digestive organs, respiratory system and intrathoracic organs, melanoma and other cancers of the skin, mesothelial and soft tissue, male genital organs, urinary tract, eye, brain and other central nervous system, thyroid and other endocrine glands, unknown, all solid cancers combined
0–49	720,000 (33)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	Lung, liver and skeletal combined*, all other solid cancers combined*
Up to 17	1,698,312 (13.6)	Continuous background radiation	Individual estimates, both direct (TLD measurements) and indirect (environmental measurements and occupancy patterns)	All solid cancers combined, nasopharynx, stomach, liver, lung

TABLE 2.2 Strengths and limitations of the main epidemiological studies of solid cancers in relation to external radiation exposures (based on UNSCEAR, 2008)

Study no.	Study	Strengths	Limitations
LOW LINEAR ENERGY TRANSFER EXPOSURES			
1	Exposures to atomic bombings		
1.1, 1.2	Life Span Study (Thompson et al, 1994; Preston et al, 2003, 2007)	Large population of all ages and both sexes not selected because of disease or occupation Wide range of doses Comprehensive individual dosimetry Survivors followed prospectively for up to 50 years or more Complete mortality ascertainment Cancer incidence ascertainment	Acute, high dose rate exposure that provides no direct information on effects of gradual low dose rate exposures Mortality follow-up commenced 5 years after exposure Incidence data from 13 to 53 years after exposure Possible effects of thermal or mechanical injury and conditions following the bombings uncertain Limited data on potential confounding factors such as smoking (*Note* This also applies to many other studies)
2	**Treatment of malignant disease**		
2.1	**Childhood exposures**		
2.1.1	International childhood cancers (Tucker et al, 1987, 1991)	Comprehensive individual dosimetry to estimate organ doses Attempt to adjust for chemotherapy Dose–response analyses	Only high dose exposures Potential for some over-matching, some hospital-based Complete dosimetry not always available
2.1.2, 2.1.8	Childhood cancers (UK) (Hawkins et al, 1996; Jenkinson et al, 2007)	Virtually complete ascertainment of incident cases within population-based cancer registries Individual estimates of radiation dose to different segments of active bone marrow Attempt to adjust for chemotherapy	Small number of cases Most of the findings relate to doses of 5 Gy or more
2.1.3	Retinoblastoma (Wong et al, 1997; Kleinerman et al, 2005a,b)	Long-term incidence follow-up Individual dose estimates for bone and soft tissue sarcoma sites Wide range of doses	Little information on chemotherapy Most of the findings concern doses of 5 Gy or more
2.1.4	Childhood cancers (France/UK) (de Vathaire et al, 1995, 1999a,b; Little et al, 1998a; Guérin et al, 2003, 2007; Menu-Branthomme et al, 2004: Guibout et al, 2005)	Incidence follow-up Doses from radiotherapy and chemotherapy estimated	Individual dose estimates generally not used in analyses Lack of external comparison group Small numbers for specific types of cancer

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
2.1.5	Childhood Hodgkin disease (Bhatia et al, 1996)	Cohort of persons exposed at young ages to high radiation doses Individual dosimetry Information available on chemotherapy doses	Small numbers of cases No formal modelling of dose–response or of chemotherapy effects
2.1.6, 2.1.7	Childhood Cancer Survivor Study (Sigurdson et al, 2005; Neglia et al, 2006; Ronckers et al, 2006)	Persons exposed at young ages to high radiation doses Individual dosimetry Information available on chemotherapy doses Large number of incident cases, relative to other studies of childhood cancer survivors	Most of the thyroid cancer findings concern doses of 10 Gy or more
2.2	**Adult exposures**		
2.2.1, 2.2.2	Cervical cancer cohort (Boice et al, 1985; Kleinerman et al, 1995)	Large-scale incidence study based on tumour registry records Long-term follow-up Relatively complete ascertainment of second cancers Unexposed comparison patients	Large doses to some organs result in cell killing and tissue damage Potential misclassification of metastatic disease for some organs Potential misclassification of exposure No individual dosimetry Characteristics of patients with cervical cancer differ from general population
2.2.3	Cervical cancer case–control (Boice et al, 1988)	Comprehensive individual dosimetry for most irradiated organs Dose–response analyses Other strengths as for the cohort study (see study 2.2.1 above)	As above, except that the problems with individual dosimetry and comparison with general population do not apply Small number of unexposed cases Potential inaccuracies in partial-body and partial-organ dosimetry
2.2.4	Lung cancer following breast cancer (Inskip et al, 1994)	Individual estimates of radiation dose to different segments of the lungs Large number of non-irradiated patients Most patients did not receive chemotherapy Substantial proportion of patients with over 20 years of follow-up	Small number of lung cancers Lack of data on individual smoking habits Potential inaccuracies in partial-body dosimetry
2.2.5, 2.2.6	Contralateral breast cancer (Boice et al, 1992; Storm et al, 1992)	Large numbers of incident cases within population-based tumour registries Individual radiation dosimetry Wide range of doses	Limited number of young females Possible over-matching of cases to controls Possible misclassification of metastases or recurrence

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
2.2.7	Soft tissue sarcoma following breast cancer (Sweden) (Karlsson et al, 1998b)	Incident cases identified from a population-based tumour registry	Analyses based on estimates of energy from radiotherapy, rather than organ dose
2.2.8	Lung cancer following Hodgkin disease (international I) (Kaldor et al, 1992)	Individual estimates of radiation dose to the affected lung Some data on individual smoking habits Detailed information on chemotherapy Relatively large number of cases	Smoking data limited, and reported more fully for cases than for controls Follow-up period generally less than 10 years
2.2.9	Lung cancer following Hodgkin disease (international II) (Travis et al, 2002; Gilbert et al, 2003)	Individual estimates of radiation dose to the affected lung Some data on individual smoking habits Detailed information on chemotherapy Large number of cases	Lack of an unexposed comparison group Possible uncertainties in estimates of radiation doses Smoking data limited
2.2.10	Breast cancer following Hodgkin disease (international) (Travis et al, 2003a, 2005a; Hill et al, 2005)	Wide range of doses to the breast Population-based cohort Detailed information on radiotherapy and chemotherapy Relatively large number of cases Females treated at relatively young ages	Lack of an unexposed comparison group Possible uncertainties in estimates of radiation doses
2.2.11	Breast cancer following Hodgkin disease (USA) (Hancock et al, 1993)	Individual assessments of doses Analyses by age at exposure	Small number of cases Limited follow-up Mostly high doses (over 40 Gy)
2.2.12	Thyroid disease following Hodgkin disease (Hancock et al, 1991)	Wide range of exposure ages	Very few cases of thyroid cancer (6) Limited follow-up (mean less than 10 years)
3	**Treatment of benign disease**		
3.1	**Exposures to children only**		
3.1.1	New York tinea capitis (Shore et al, 2002, 2003)	Relatively good dose ascertainment for skin and other cancers	Small number of cancers at sites other than skin Few females
3.1.2	Israeli tinea capitis (Ron et al, 1988, 1989, 1991; Sadetzki et al, 2005, 2006)	Large number exposed Two control groups Ascertainment of cancer from hospital records and tumour registry Individual dosimetry for many organs	Dosimetry sometimes uncertain, owing to possible patient movement or uncertainty in tumour location Limited dose range

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
3.1.3	Rochester thymic irradiation (Hildreth et al, 1985, 1989; Shore et al, 1993)	Individual dosimetry for thyroid and some other sites Sibling control group Long follow-up Effects of multiple radiation exposures could be evaluated Dose–response analyses undertaken	Radiation treatment fields for newborns varied, and dosimetry uncertain for some sites Adjustment in analysis for sibship size uncertain Questionnaire follow-up may have resulted in under-ascertainment of cases
3.1.4	Tonsil irradiation (Schneider et al, 1985; 1993, 1998, 2008)	Individual dosimetry for thyroid and some other sites Long follow-up Large numbers of cases for certain sites Dose–response analyses	Effect of screening on ascertainment of thyroid cancer and nodules No unexposed control group
3.1.5	Tonsil, thymus or acne irradiation (DeGroot et al, 1983)	Long period between exposure and examination Prospective as well as retrospective follow-up	Possible screening effect Small cohort No unexposed control group
3.1.6	Thymus adenitis screening (Maxon et al, 1980)	Information on childhood exposure Availability of unexposed control group	Relatively few thyroid cancers (16) Individual dose estimates not available
3.1.7	Lymphoid hyperplasia screening (Pottern et al, 1990)	Individual dosimetry Comparison of questionnaire and clinical examination results Comparison group treated by surgery for the same condition	Apparent bias in questionnaire data, owing to self-selection of subjects Clinical examinations provide data on prevalence rather than incidence Study of thyroid nodules; cancer cases not confirmed
3.1.8, 3.1.9	Childhood skin haemangioma: (Sweden) (Lundell, 1994; Lundell et al, 1994, 1996; Lundell and Holm, 1995; Lindberg et al, 1995; Karlsson et al, 1998a)	Long-term and complete follow-up Comprehensive individual dosimetry for many organs Incidence ascertained Protracted exposure to radium plaques	Relatively small numbers for specific cancers
3.1.10	Childhood skin haemangioma (France) (Dondon et al, 2004)	Individual dosimetry Organ doses available Unexposed comparison group Long follow-up	Dose–response relationship not calculated due to low number of cancer deaths

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
3.2	**Exposures to females only**		
3.2.1, 3.2.2, 3.2.5	Benign gynaecological disease (Ryberg et al, 1990; Darby et al, 1994; Inskip et al, 1990)	Large number exposed Unexposed females with benign gynaecological disease Long mortality follow-up Individual dosimetry Protracted exposure to radium implants (10–24 hours) in study 3.2.1 Dose–response analyses	Uncertainty in proportion of active bone marrow exposed Small numbers of particular cancers Misclassification of certain cancers on death certificates (eg pancreas)
3.2.3	New York acute post-partum mastitis (Shore et al, 1986; Shore, 1990)	Individual estimates of breast dose from medical records Breast cancer incidence ascertained Dose–response analyses	All exposed females were parous, but comparison females were not (380 unexposed and sisters of both exposed and unexposed) Inflamed and lactating breast might modify radiation effect
3.2.4	Benign breast disease (Sweden) Mattson et al, 1997)	Incidence study with long-term follow-up Individual dosimetry for many organs Multiple radiation exposures Unexposed control group	Lack of data on potential confounders Small numbers of cases
3.3	**Exposures to males and females**		
3.3.1	Ankylosing spondylitis (Weiss et al, 1994)	Large number of exposed patients Long-term and complete mortality follow-up	Comparisons with general population Underlying disease related to colon cancer and possibly other conditions Individual dose estimates available only for a 1 in 15 sample of the population
3.3.2	Peptic ulcer (Griem et al, 1994; Carr et al, 2002)	Individual dosimetry Unexposed patients with peptic ulcer Exceptionally long follow-up (over 50 years) Some risk information available in records	Standardised radiotherapy precluded dose–response analyses Inhomogeneous dose distribution within organs – simple averaging may be misleading Metastatic spread of stomach cancer probably misclassified as liver and pancreatic cancer on death certificates Possible selection of somewhat unfit patients for radiotherapy rather than surgery

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
4	**Diagnostic examinations**		
4.1, 4.2	Massachusetts TB fluoroscopy (Davis et al, 1989; Shore et al, 1990; Boice et al, 1991)	Incidence study with long-term follow-up (50 years) Individual dosimetry based on patient records and measurements Unexposed TB patients Multiple radiation exposures over many years Dose–response analyses	Uncertainty in dose estimates related to fluoroscopic exposure time and patient orientation Questionnaire response probably under-ascertained cancers Debilitating effect of TB may have modified radiation effects for some sites, eg lung
4.3	TB fluoroscopy (Canada) (Howe, 1995; Howe and McLaughlin, 1996)	Large number of patients Unexposed TB comparison group Individual dosimetry for lung and female breast Multiple radiation exposures over many years Dose–response analyses	Mortality limits comparisons with breast cancer incidence series, eg time response Uncertainties in dosimetry limit precise quantification of risk Different dose responses for female breast cancer between one sanatorium and the rest of Canada may indicate errors in dosimetry, differential ascertainment, or differences in biological response
4.4	Scoliosis (Doody et al, 2000)	Adolescence possibly a vulnerable age for exposure Dosimetry undertaken based on number of films and breast exposure Dose–response analysis	Comparison with general population potentially misleading, since scoliosis is associated with several breast cancer risk factors (eg nulliparity) Dose estimates may be subject to bias as well as random error
4.5	Diagnostic X-rays (Sweden) (Inskip et al, 1995)	Information on diagnostic X-rays over many years abstracted from medical records	Analyses based on number and type of X-ray procedures, rather than actual doses
4.6	Occupational X-rays (Boffetta et al, 2005)	Trend analysis with total X-ray examinations Analyses adjusts for confounding effect of smoking	Self-reported X-ray examinations Analyses based on the number of X-ray procedures, rather than actual doses
4.7	Los Angeles medical and dental X-rays (Preston-Martin et al, 1988)	Dosimetry attempted based on number and type of examinations	No available records of X-rays Potential for recall bias in dose ascertainment Doses likely to have been underestimated
4.8	Dental X-rays (Washington state) (Longstreth et al, 2004)	Two controls per case	Self-reported X-ray examinations Analyses based on the number and type of examination rather than actual doses

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
5	**Prenatal exposures**		
5.1	Oxford Survey of Childhood Cancers (Stewart et al, 1958; Bithell and Stewart, 1975; Knox et al, 1987)	Large numbers of cancers Comprehensive evaluation of potential confounding Early concerns over response bias and selection bias resolved	Uncertainty in fetal doses Similar relative risks for leukaemia and solid cancers – points to possible residual confounding
5.2	New England childhood cancers (Monson and MacMahon, 1984)	Large numbers Reliance upon obstetric records to determine exposure	Uncertainty in fetal doses
5.3	Survivors of atomic bombings (Delongchamp et al, 1997; Preston et al, 2008)	Not selected for exposure Reasonably accurate dose estimates Mortality follow-up relatively complete Follow-up until adulthood	Small number of exposed individuals and small number of cases Incidence determination may not be complete Mechanical and thermal effects may have influenced results
6	**Occupational exposures**		
6.1, 6.2	Nuclear workers (multi-country studies) (Cardis et al, 1995, 2005b, 2007; Vrijheid et al, 2007)	Large numbers of workers Personal dosimetry Low dose protracted and multiple exposures	Low doses make demonstration of radiation effect difficult Possible confounding effect of chemicals and other agents in the workplace and also smoking Healthy worker effect Mortality follow-up Lifestyle factors (eg smoking histories) not available
6.3	Nuclear workers (Japan) (Iwasaki et al, 2003)	Large number of workers Personal dosimetry Low dose protracted and multiple exposures Some information from questionnaires on lifestyle factors and on exposure to other agents in the workplace	Complex follow-up procedures meant that analyses focused on a subset of workers with a short period of prospective follow-up Healthy worker effect Mortality follow-up Not possible to adjust for other exposures to other agents, lifestyle factors or socioeconomic status in analyses
6.4	National Dose Registry of Canada (Sont et al, 2001)	Large number of workers Personal dosimetry Low dose protracted and multiple exposures Incidence follow-up	Possible confounding effect of agents in the workplace Strong healthy worker effect Lifestyle factors (eg smoking histories) not available Suggestions of problems in linkage of dose registry to follow-up data

TABLE 2.2 ***continued***

Study no.	Study	Strengths	Limitations
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	Large number of workers Personal dosimetry Low dose protracted and multiple exposures Incidence and mortality follow-up	Low doses make demonstration of radiation effect difficult for specific cancers Possible confounding effect of chemicals and other agents in the workplace Healthy worker effect Lifestyle factors (eg smoking histories) not available
6.6	Portsmouth naval shipyard: lung cancer study (Yiin et al, 2007)	Large number of lung cancer cases Personal dosimetry Low dose protracted and multiple exposures Adjustment made for potential exposure to welding fumes and asbestos, as well as for work-related medical X-ray examinations	Mortality ascertainment of cases Smoking histories not available
6.7, 6.8	Chernobyl clean-up workers (Ivanov et al, 2002, 2004, 2008, 2009; Rahu et al, 2006)	Often large numbers Low dose protracted and multiple exposures Could provide useful information in future	Difficulties in assessing individual exposures Possible differences in cancer ascertainment relative to the general population Relatively short period of follow-up so far (now extended for later thyroid analysis)
6.9	Mayak workers (Shinikova et al, 2003)	Wide range of exposures Individual measurements of external gamma dose and plutonium body burden	Possible uncertainties in assessments of exposures
7	**Natural radiation**		
7.1	Yangjiang (Sun et al, 2000; Tao et al, 2000)	Large cohorts in high background and control areas Stable population Extensive dosimetry for region Assessment of potential confounders	Mortality follow-up Data not available on migration from the study areas during the early part of the study Small number of cases Low doses

TABLE 2.3 Main epidemiological studies of solid cancers in relation to internal radiation exposures (based on UNSCEAR, 2008)

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
LOW LINEAR ENERGY TRANSFER EXPOSURES				
8	**Medical exposures**			
8.1	Diagnostic iodine-131 (Holm et al, 1989; Dickman et al, 2003)	Cohort (incidence)	36,792 exposed persons 80% female Age: 1–75 (43) [b]	Sweden
8.2	Hyperthyroidism iodine-131 (Holm et al, 1991; Hall et al, 1992)	Cohort (incidence/ mortality)	10,522 exposed persons 82% female Age: 13–70	Sweden
8.3	Thyrotoxicosis (Ron et al, 1998)	Cohort (incidence/ mortality)	23,020 exposed persons 12,573 unexposed persons 79% female Age: 0–>60 (mean 46)	USA
8.4	Iodine-131 hyperthyroidism (Franklyn et al, 1999)	Cohort (incidence/ mortality)	7,417 exposed persons 83% female Age: ≤49–≥70 (57)	UK
8.5	Iodine-131 thyroid cancer patients (Rubino et al, 2003)	Cohort (incidence)	6,676 patients 4,225 treated with iodine-131 1,194 treated with external beam radiotherapy (9% received both types of treatment)	France, Italy, Sweden

Table 2.3 extends on to the facing page and continues for eight pairs of pages

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
2–47	886,618 (24.1)	Diagnostic iodine-131	Individual values of activity administered; organ dose estimates for thyroid	Thyroid, all other sites
1–26	139,018 (13.2)	Treatment of hyper-thyroidism	Average administered activity (multiple treatments)	Oral cavity and pharynx, salivary glands, oesophagus*, stomach*, colorectal, liver, pancreas, respiratory tract*, breast (females), genital organs (separately for females and males), kidney*, bladder, nervous system, brain*, thyroid*, other endocrine sites [c]
0–45	738,831 (20.8)	Treatment of hyper-thyroidism	Individual values of activity administered; organ dose estimates	Buccal cavity, oesophagus, stomach, colorectal, liver, pancreas, larynx, lung*, breast (females)*, all uterus, ovary, prostate, bladder, kidney*, brain and other central nervous system tumours, thyroid*
1–≥20	72,073 (9.7)	Treatment of hyper-thyroidism	Individual values of activity administered	Thyroid*, bladder, uterine, small bowel*, all other sites
2–55	n.a. (13)	Treatment of thyroid cancer	Individual values of iodine-131 activity administered	All solid cancers combined*, soft tissue and bone*, colorectal*, breast

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
9	**Environmental exposures**			
9.1	**Environmental exposures: Chernobyl**			
9.1.1	Belarus (Astakhova et al, 1998)	Case–control (incidence)	107 cases 107 population-based controls plus 107 controls matched by 'pathways to diagnosis' of cases Both sets of controls matched by sex, age and region of residence at time of accident 52% female Age at accident: 0–16	Belarus
9.1.2	Russian Federation – Bryansk (Davis et al, 2004a; Kopecky et al, 2006)	Case–control (incidence)	26 cases 52 population-based controls, matched by sex, birth year, area of residence and type of settlement at time of accident 50% female Age at time of accident: 0–19	Russian Federation
9.1.3	Belarus and Russian Federation (Cardis et al, 2005a)	Case–control (incidence)	276 cases 1,300 population-based controls, matched by sex, age and region of residence at time of accident 63% female Age at accident: 0–14	Belarus, Russian Federation

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 6	n.a.	Internal exposure to radioactive iodine, plus internal and external exposure from other radionuclides, in areas contaminated by the Chernobyl accident	Iodine-131 dose estimated from ground deposition of caesium-137 and iodine-131, contemporary thyroid radiation measurements, and from questionnaires and interviews	Thyroid*
5–11	n.a.	Internal exposure to radioactive iodine, plus internal and external exposure from other radionuclides, in areas contaminated by the Chernobyl accident	Dose reconstruction based on semi-empirical model, incorporating data on contamination levels and data on the subject's dietary habits, etc, collected in interviews conducted primarily with mothers	Thyroid*
6–12	n.a.	Internal exposure to radioactive iodine, plus internal and external exposure from other radionuclides, in areas contaminated by the Chernobyl accident	Dose reconstruction based on location and dietary habits at the time of the accident and subsequently, likely stable iodine status at the time of the accident, and information on levels of contamination in settlements	Thyroid*

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
9.1.4	Ukraine (Tronko et al, 2006)	Cohort (prevalence)	13,127 individuals, aged <18 years and resident in the most heavily contaminated areas at the time of the accident, who were screened for thyroid pathology during 1998–2000 50.7% female	Ukraine
9.2	**Environmental exposures: Techa River**			
9.2.1	Techa River population (Kossenko et al, 2005; Krestinina et al, 2005)	Cohort (mortality)	29,873 people born before 1950 who lived near the Techa River between 1950 and 1960 and who were exposed to radioactive releases from the Mayak plant 60% female 20% Tartars/Bashkirs	Russian Federation
9.3	**Environmental exposures: Hanford**			
9.3.1	Hanford (Davis et al, 2004b; Kopecky et al, 2004)	Cohort (incidence/ prevalence)	3,440 persons born in eastern Washington State during 1940–46 who were exposed to iodine-131 released from the Hanford nuclear site during 1944–57 and who were examined for thyroid disease during 1992–97	USA
9.4	**Environmental exposures: weapons fallout**			
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	Cohort (mortality)	9,850 residents of exposed villages 9,604 residents of comparison villages 50% female Age at main exposure: *in utero* – >40	Kazakhstan

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
12–14	n.a.	Internal exposure to radioactive iodine, plus internal and external exposure from other radionuclides, in areas contaminated by the Chernobyl accident	Direct measurements of activity in thyroid, mostly made 10–60 days after the accident, plus information on individuals' dietary and lifestyle habits	Thyroid*
Up to 50	865,812 (29.0)	Internal and external exposures to radioactive waste discharged by nuclear weapons production plant	Dose reconstruction based on environmental measurements of gamma dose rate and whole-body counting	All solid cancers combined (excluding bone)
Five-year period several decades after exposure; information also available on earlier cases	n.a.	Internal exposure to radioactive iodine	Dose reconstruction based on assessments of iodine concentrations in the environment and on residential and dietary histories supplied by those in the study	Thyroid
11–50	582,750 (30.0)	Internal and external exposure from fallout from atmospheric nuclear weapons testing	Dose reconstruction based on historical environmental monitoring data, residential histories, etc	Digestive and peritoneum*, respiratory and intrathoracic*, oesophagus, stomach*, liver, lung*, breast (females), all solid cancers*

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
9.4.2	Marshall Islands fallout (Hamilton et al, 1987, 1989; Robbins et al, 1989)	Prevalence	2,273 exposed persons 55% female Age: 5–>60	Marshall Islands
9.4.3	Utah iodine-131 fallout: thyroid disease (Lyon et al, 2006)	Prevalence	2,496 persons	USA
10	**Occupational exposures**			
10.1	UK Atomic Energy Authority: prostate cancer study (Rooney et al, 1993)	Case–control	136 cases 404 controls Males Age at diagnosis: <65–>75 14% of subjects with documented internal exposure	UK
HIGH LINEAR ENERGY TRANSFER EXPOSURES				
11	**Treatment of benign disease**			
11.1	Radium-224 TB and ankylosing spondylitis patients (Heinrichs et al, 1995; Nekolla et al, 1995, 1999, 2000; Spiess et al, 1995)	Cohort (incidence)	899 exposed persons 31% female 24% aged <20 years	Germany
11.2	Radium-224 ankylosing spondylitis patients (Wick et al, 1995, 1999)	Cohort (incidence)	1,577 exposed persons 1,462 unexposed persons	Germany
12	**Diagnostic examinations**			
12.1	Thorotrast patients (van Kaick et al, 1989, 1995, 1999; Becker et al, 2008)	Cohort (mortality)	2,326 exposed persons 1,890 unexposed persons 26% female	Germany, Austria

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
29–31	n.a.	Short-lived radionuclides from nuclear explosion	Estimated average dose; distance was also used as a surrogate	Thyroid
12–17 and 32–33 [d]	n.a.	Fallout from nuclear weapons tests	Based on residence histories and fallout deposition records	Thyroid*
n.a.	n.a.	Exposures in nuclear fuel cycle and research	Urine measurements and whole-body monitoring	Prostate*
0–54	23,400 (28.8) [e]	Injection with radium-224	Internal dosimetric calculations based on amount injected	Bone*, breast (females)*, connective tissue*, liver*, kidney*, thyroid*, ovary, pancreas, all uterus, prostate, bladder*, stomach, colon, lung
0–51	63,500 (20.9)	Injection with radium-224	Information on amount injected	Bone and connective tissue, stomach, liver, lung, urinary system, breast (females)
3–>50	n.a.	Injection with Thorotrast	Hospital records of amounts injected; CT measurements of some patients	Liver*, extrahepatic bile ducts*, gallbladder, pancreas*, larynx, bone sarcoma, lung, mesothelioma, kidney, bladder, prostate, adrenal, brain, GI tract

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
12.2	International Thorotrast cohort (Travis et al, 2003b)	Cohort (incidence/ mortality)	1,736 exposed persons 1,407 unexposed persons 45% female Age <20–>60 (mean 33.9)	Denmark, Sweden, USA
12.3	Thorotrast patients (dos Santos Silva et al, 1999, 2003)	Cohort (mortality)	1,096 exposed persons 1,014 unexposed persons 38% female Age <20–79	Portugal
13	**Occupational exposures**			
13.1	**Occupational exposure: radium**			
13.1.1	Radium luminisers (Stebbings et al, 1984, 1989; Stehney, 1995; Rowland, 1995)	Cohort (incidence/ mortality)	2,543 females	USA
13.1.2	Radium luminisers (Baverstock et al, 1981; Baverstock and Papworth, 1989)	Cohort (mortality)	1,203 females	UK
13.2	**Occupational exposure: plutonium**			
13.2.1	Mayak plutonium workers (Gilbert et al, 2000; 2004; Koshurnikova et al, 2000; Shilnikova et al, 2003; Sokolnikov et al, 2008)	Cohort (mortality)	5,859 workers monitored for plutonium 15,597 other workers 24% female Age at hire: 15–>40 [g]	Russian Federation

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
2–>50	37,542 (26.6)	Injection with Thorotrast during cerebral angiography	Volume of Thorotrast injected (available for 80% of patients) times length of exposure	All cancers combined*, oral cavity, pharynx, stomach, small intestine, large intestine, liver*, bile ducts*, gallbladder*, pancreas*, peritonium and other digestive*, lung, bone, melanoma of skin, non-melanoma skin, breast (females), uterine cervix, uterine body, ovary*, prostate*, testis, bladder, kidney*, brain and other central nervous system
0–>50	13,283 (22.2) for exposed persons 15,407 (25.2) for unexposed persons [f]	Injection with Thorotrast, mainly during cerebral angiography	Volume of Thorotrast injected (available for 92% of the systematically exposed patients)	Liver*, lung, bone, breast (females), brain
0–71.5	119,020 (46.8)	Ingestion of radium-224 and -226	Body burdens of about 1,500 females assessed by measurement of gamma rays and/or exhaled radon; used for calculation of systemic intake and skeletal dose	Bone, stomach, pancreas, colon, rectum, liver, lung, breast, cervix, and corpus uteri
Up to 47	44,883 (37.3)	Work with radium	Measurements of radium-226 content in 470 luminisers; measurements of gamma doses for some luminsers	All cancers other than breast combined, breast (females), osteosarcoma
Up to 52	670,478 (31.2)	Exposures in plutonium production or radiochemical plants	Bioassays for plutonium and recorded external radiation doses	Liver, lung, bone

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
13.2.2	Sellafield workers (Omar et al, 1999)	Cohort (incidence/ mortality)	5,203 plutonium workers (4,609 of whom had plutonium dose assessed) 5,179 other radiation workers 4,003 non-radiation workers 19% female	UK
13.2.3	Los Alamos workers (Wiggs et al, 1994)	Cohort (mortality)	3,775 males with plutonium body burden of 74 Bq or more 11,952 males with lower body burdens	USA
13.2.4	Rocky Flats: cohort study (Wilkinson et al, 1987)	Cohort (mortality)	5,413 males with external and/or plutonium exposures	USA
13.2.5	Rocky Flats: lung cancer study (Brown et al, 2004)	Case–control (mortality)	180 cases 720 controls 98 cases and 412 controls with internal lung dose Median age at first internal lung dose: 49 (cases), 47 (controls) 4% female	USA
13.2.6	Hanford workers (Wing et al, 2004)	Cohort (mortality)	33,459 workers (25,314 males, 8,145 females)	USA
13.3	**Occupational exposure: various**			
13.3.1	Nuclear industry workers (Carpenter et al, 1998)	Cohort (mortality)	17,605 workers monitored for internal exposure 23,156 other radiation workers 8% female	UK

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 46 for mortality; up to 40 for incidence	415,432 (29)	Exposures to plutonium in nuclear fuel cycle and research	Red bone marrow dose assessed using measurement of plutonium in urine Recorded exposures to external radiation	Stomach, colon, pancreas, lung, pleura, breast (females)*, prostate, bladder, brain and other central nervous system, ill-defined and secondary*
Up to 47	456,637 (29)	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Oral cancers, stomach, colon, rectum, pancreas, lung, bone, prostate, bladder, kidney, brain and central nervous system, all cancers combined
Up to 28	52,772 (9.7)	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Oesophagus, stomach, colon, liver, pancreas, lung, all skin, prostate, bladder, kidney, all brain tumours, all cancers combined
n.a.	n.a.	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	Lung
10–40	n.a.	Exposures to plutonium in nuclear fuel cycle and research	Measurement of plutonium in urine Recorded exposures to external radiation	All cancers, cancers of tissues where plutonium deposits, lung, digestive cancer, brain
Up to 43	1,020,000 (25)	Exposures in nuclear fuel cycle and research	Records of monitoring for internal exposure Recorded exposures to external radiation	Buccal cavity and pharynx, oesophagus, stomach, small intestine, large intestine, rectum, liver and gallbladder, pancreas, nasal cavities and sinuses, lung, pleura, bone, connective tissue, all skin, breast (females), all uterus, ovary, prostate, testis, bladder, kidney, brain and other central nervous system, thyroid, all malignant neoplasms combined

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
13.3.2	Oak Ridge: Y-12 plant (Richardson and Wing, 2006)	Cohort (mortality)	3,864 workers monitored for internal exposure	USA
13.4	**Occupational exposure: radon**			
13.4.1	Combined analysis of lung cancer in radon-exposed miners (Lubin et al, 1995)	Cohort (mortality)	11 miner cohorts, 65,000 males	Worldwide
13.4.2	Combined analysis of cancers other than lung in radon-exposed miners (Darby et al, 1995)	Cohort (mortality)	11 miner cohorts 64,209 males	Worldwide
13.4.3	Uranium miners (Grosche et al, 2006; Kreuzer et al, 2008)	Cohort (mortality)	59,000 male Wismut company miners	Germany
14	**Environmental exposures**			
14.1	**Environmental exposures: radon in homes**			
14.1.1	European pooling (Darby et al, 2005a, 2006)	Case–control (incidence)	7,148 cases 14,208 controls (mixture of population and hospital based) 27% female [h] Age: <45–≥75	Austria, Czech Republic, Finland, France, Germany, Italy, Spain, Sweden, UK
14.1.2	North American pooling (Krewski et al, 2005, 2006)	Case–control (incidence)	3,662 cases 4,966 population-based controls, matched by age, sex and region 72% female[g] Age: <60–≥75	Canada, USA
14.1.3	Chinese pooling (Lubin et al, 2004b)	Case–control (incidence)	1,050 cases 1,996 population-based controls, matched by age, sex and region 38% female [g] Age: <45–≥75	China

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 44	n.a.	Exposures in nuclear fuel cycle and research	Records of monitoring for internal exposure Recorded exposures to external radiation	Lung
n.a.	1,200,000	Exposure to radon decay products	Each cohort required to provide Individual estimates (actual methods for each cohort not specified)	Lung
Up to 28	1,200,000	Exposure to radon decay products	Each cohort required to provide Individual estimates (actual methods for each cohort not specified)	All non-lung cancers combined and 28 individual cancer categories
5–43	1,800,000 (30.5)	Exposure to radon decay products	Derived from job-exposure matrix	Lung and 24 other individual solid cancer categories
n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung*
n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung*
n.a.	n.a.	Radon in homes	Track-etch detector measurements in homes occupied by subjects	Lung*

The notes to the table are given on p 66

TABLE 2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
14.2	**Environmental exposures: radon and other radionuclides in drinking water**			
14.2.1	Drilled well users (Auvinen et al, 2005; Kurttio et al, 2006)	Case–cohort (incidence)	88 stomach cancer cases, 61 bladder cancer cases, 51 kidney cancer cases and 274 reference persons	Finland

Notes

a An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a statistically significantly higher proportion of the cases were exposed to radiation (case–control studies).
b Age at first exposure, mean in parentheses.
c Significance tests based on 10-year survivors.
d Periods of thyroid examinations, relative to the peak fallout in 1953.
e Figures quoted are for 812 persons with complete information.
f Values based on follow-up over the period five years or more following the first examination.
g Values cited by Gilbert et al (2004).
h Value for controls.

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
n.a.	n.a.	Radon, radium-226 and uranium in drinking water	Measurement of activity concentrations in drinking water	Stomach, bladder, kidney

TABLE 2.4 Strengths and limitations of the main epidemiological studies of solid cancers in relation to internal radiation exposures (based on UNSCEAR, 2008)

Study no.	Study	Strengths	Limitations
LOW LINEAR ENERGY TRANSFER EXPOSURES			
8	**Medical exposures**		
8.1	Diagnostic iodine-131 (Holm et al, 1989; Dickman et al, 2003)	Large numbers Unbiased and nearly complete ascertainment of cancers through linkage with cancer registry Administered activities of iodine-131 known for each patient Organ doses to the thyroid computed with some precision Dose–response analysis for thyroid cancer, based on wide range of doses Low dose rate exposure	Comparison with general population only, except for thyroid cancer Reason for some examinations related to high detection of thyroid cancers, ie suspicion of thyroid tumour was often correct Low doses to organs other than thyroid Population under surveillance
8.2	Hyperthyroidism iodine-131 (Sweden) (Holm et al, 1991; Hall et al, 1992)	Large numbers Nearly complete incidence ascertainment Administered activities of iodine-131 known	Comparison with general population Dose–response not based on organ doses Risks at high doses may have been reduced owing to cell killing Patients selected for treatment
8.3	Thyrotoxicosis patients (USA) (Ron et al, 1998)	Large numbers of patients treated with iodine-131 Large unexposed comparison groups Comprehensive follow-up effort Administered activities of iodine-131 known	Individual doses computed only for certain organs Mortality follow-up Few patients irradiated at young ages Possibility of selection bias by treatment
8.4	Iodine-131 hyperthyroidism (UK) (Franklyn et al, 1999)	Incidence and mortality follow-up via national registers Administered activities of iodine-131 known	Comparison with general population Dose–response not based on organ doses Patients selected for treatment
8.5	Iodine-131 thyroid cancer patients (France, Italy and Sweden) (Rubino et al, 2003)	Incidence follow-up Administered activities of iodine-131 known Unexposed group	Individual doses not computed Small numbers for some specific cancer types Few patients irradiated at young ages Possibility of selection bias by treatment

TABLE 2.4 ***continued***

Study no.	Study	Strengths	Limitations
9	**Environmental exposures**		
9.1.1–9.1.4	Chernobyl-related exposure (Astakhova et al, 1998; Davis et al, 2004a; Cardis et al, 2005a; Kopecky et al, 2006; Tronko et al, 2006)	Large numbers exposed Wide range of thyroid doses within the states of the former Soviet Union	Mixture of radioiodines and availability of data make dose estimation difficult, particularly for individuals Possible differences in cancer ascertainment relative to the general population
9.2.1	Techa River population (Kossenko et al, 2005; Krestinina et al, 2005)	Large numbers with relatively long follow-up Wide range of estimated doses up to 0.45 Gy Unselected population; attempted use of local population rates for comparison Possible to examine ethnic differences in cancer risk Potential for future	Dosimetry difficult and not individual Mixture of internal and external exposures complicates dosimetry Follow-up and cancer ascertainment uncertain Number of site-specific cancer cases currently small
9.3.1	Hanford (Davis et al, 2004b; Kopecky et al, 2004)	Detailed efforts to reconstruct exposures Study had sufficient statistical power to detect risks of the level that might have been expected	Small numbers of cases Problems in reconstructing exposures several decades subsequently
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	Long-term prospective follow-up Sizeable numbers of cancers Estimates made of individual doses in the exposed group	Substantial emigration from study region during the 1990s Possible bias in selection of comparison group; also lack of individual doses in this group Potential discrepancy between doses assessed using physical and biological techniques Mortality follow-up
9.4.2	Marshall Islands fallout (Hamilton et al, 1987, 1989; Robbins et al, 1989)	Population unselected for exposure Comprehensive long-term medical follow-up Individual dosimetry attempted	Mixture of radioiodines and gamma radiation preclude accurate dose estimation Surgery and hormonal therapy probably influenced subsequent occurrence of thyroid neoplasms Small numbers
9.4.3	Utah iodine-131 fallout: thyroid disease (Lyon et al, 2006)	Comprehensive dosimetry attempted Protracted exposures at low dose rate	Possible recall bias in consumption data used for risk estimation Possible under-ascertainment of disease in low dose subjects Small number of thyroid cancers

TABLE 2.4 ***continued***

Study no.	Study	Strengths	Limitations
10	**Occupational exposures**		
10.1	UK Atomic Energy Authority: prostate cancer study (Rooney et al, 1993)	Information abstracted for study subjects on socio-demographic factors, exposures to radionuclides, external doses and other substances in the workplace Cases and controls selected from an existing cohort	Exposure to some radionuclides tended to be simultaneous, making it difficult to study them individually
HIGH LINEAR ENERGY TRANSFER EXPOSURES			
11	**Treatment for benign disease**		
11.1, 11.2	Radium-224 patients (Heinrichs et al, 1995; Nekolla et al, 1995, 1999, 2000; Spiess et al, 1995; Wick et al, 1995, 1999)	Long-term follow-up Substantial proportion of patients treated in childhood or adolescence	Uncertainties in organ doses for individual patients Other aspects of treatment may be relevant (eg X-rays) Comparison group constructed only recently for Spiess et al (1995)
12	**Diagnostic examinations**		
12.1–12.3	Thorotrast patients (van Kaick et al, 1989, 1995, 1999; dos Santos Silva et al, 1999, 2003; Travis et al, 2003b; Becker et al, 2008)	Long-term follow-up	Uncertainties in organ doses for individual patients Chemical attributes of Thorotrast might influence risks Many of the hospital patients in the comparison group in study 12.1 had unspecified or unknown diagnoses
13	**Occupational exposures**		
13.1.1	Radium luminisers (Stebbings et al, 1984, 1989; Stehney, 1995; Rowland, 1995)	Protracted exposures from radium-226 Long-term follow-up	Potential inaccuracies in estimating radium intakes Distribution of radium in bone may not be uniform
13.2.1	Mayak plutonium workers (Gilbert et al, 2000; 2004; Koshurnikova et al, 2000; Shilnikova et al, 2003; Sokolnikov et al, 2008)	Wide range of exposures Individual measurements of plutonium body burden and external gamma dose	Uncertainties in assessment of plutonium exposures

TABLE 2.4 ***continued***

Study no.	Study	Strengths	Limitations
13.2.2–13.2.6, 13.3.1, 13.3.2	Nuclear workers (UK and USA) (Wilkinson et al, 1987; Wiggs et al, 1994; Carpenter et al, 1998; Omar et al, 1999; Brown et al, 2004; Wing et al, 2004; Richardson and Wing, 2006)	Individual measurements of plutonium body burden or other internally deposited radionuclides, and external gamma dose	General lack of information on smoking and other potential non-radiation confounders (does not apply to study 13.2.5) Possible uncertainties in assessment of exposures
13.4.1–13.4.3	Radon-exposed underground miners (Darby et al, 1995; Lubin et al, 1995; Grosche et al, 2006; Kreuzer et al, 2008)	Large numbers Protracted exposures over several years Wide range of cumulative exposures Exposure–response analyses	Uncertainties in assessment of early exposures Possible modifying effect of other types of exposure in mines Smoking histories limited or not available
14	**Environmental exposures**		
14.1.1–14.1.3	Radon in homes (Lubin et al, 2004b; Darby et al, 2005a, 2006; Krewski et al, 2005, 2006)	Protracted exposures over many years Individual data on radon levels and, to a very detailed level, on smoking Increased precision and ability to analyse modifying factors through combined analyses	Radon concentrations low for many subjects
14.2.1	Radon and other radionuclides in drinking water (Auvinen et al, 2005; Kurttio et al, 2006)	Some information on smoking	Limited statistical power due to small number of cases

Annex to Chapter 2

Epidemiological Studies of Radiation Risk: Less Informative Studies of Solid Cancers Risks

TABLE A2.1 Less informative epidemiological studies of solid cancers in relation to external radiation exposures (based on UNSCEAR, 2008)

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
LOW LINEAR ENERGY TRANSFER EXPOSURES				
1	**Exposures to atomic bombings**			
A1.1	Exposure to ionising radiation in adulthood and thyroid cancer incidence (Richardson, 2009)	Cohort	Life Span Study incidence data restricted to those over 20 year at time of bombing 21,331 males and 38,356 females	Japan
A1.2	Incidence of female breast cancer, 1950–90 (Land et al, 2003)	Cohort	Life Span Study incidence data from the LSS-E85 sample 70,165 females	Japan
2	**Treatment of malignant disease**			
2.2	**Adult exposures**			
A2.2.1	Soft tissue and bone sarcoma following breast cancer (Rubino et al, 2005)	Case–control (incidence) within a cohort of 6,597 females	14 cases, 98 controls	France
A2.2.2	Lung cancer following Hodgkin disease (van Leeuwen et al, 1995)	Case–control (incidence) within a cohort of 1,939 patients	30 cases, 82 controls 101 exposed persons 11 unexposed persons 4% female Age: <45–>55 (mean 49.4)	Netherlands
A2.2.3	Breast cancer following Hodgkin disease (van Leeuwen et al, 2003)	Case–control (incidence) within a cohort of 770 patients	48 cases, 175 controls 220 exposed females 3 unexposed females Age: <41	Netherlands
6	**Occupational exposures**			
A6.1	UK Atomic Weapons Establishment (Beral et al, 1988; Carpenter et al, 1994)[b]	Cohort (mortality)	9,389 monitored workers 12,463 other workers 9% female	UK
A6.2	UK Atomic Energy Authority (Fraser et al, 1993; Carpenter et al, 1994; Atkinson et al, 2004, 2007)	Cohort (incidence/ mortality)	26,395 monitored workers 25,961 other workers 29% female 2,956 cancer deaths	UK

Table A2.1 extends on to the facing page and continues for four pairs of pages

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
48 years	1,377,003	Direct radiation from Hiroshima and Nagasaki atomic bomb explosions	Individual reconstructed dose	Thyroid
50 years	n.a.	Direct radiation from Hiroshima and Nagasaki atomic bomb explosions	Individual reconstructed dose (DS86)	Breast
n.a.	n.a.	Radiotherapy	Individual doses from therapy records	Soft tissue and bone sarcoma*
1–23	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Lung*
5–>25	n.a.	Radiotherapy	Individual doses from therapy records and experimental measurements	Breast cancer (females)*
Up to 37	216,000 [c] (23)	Weapons research	Recorded exposures to external radiation	35 cause of death groupings including all major cancers
Up to 51	1,370,000 (26.7)	Nuclear and reactor research and fuel processing	Recorded exposures to external radiation	35 cause of death groupings including all major cancers

The notes to the table are given on p 80

TABLE A2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
A6.3	Sellafield (Carpenter et al, 1994; Douglas et al, 1994) [b]	Cohort (incidence/ mortality)	10,028 monitored workers 3,711 other workers 19% female	UK
A6.4	Springfields (McGeoghegan and Binks, 2000a)	Cohort (incidence/ mortality)	13,960 monitored workers 5,489 other workers 12% female	UK
A6.5	Capenhurst (McGeoghegan and Binks, 2000b)	Cohort (incidence/ mortality)	3,244 monitored workers, 3% female 9,296 other workers, 14% female	UK
A6.6	Chapelcross (McGeoghegan and Binks, 2001) [b]	Cohort (incidence/ mortality)	2,209 monitored workers, 6% female 419 other workers, 61% female	UK
A6.7	Hanford (Wing and Richardson, 2005) [d]	Cohort (mortality)	26,389 monitored workers 25% female	USA
A6.8	Rocky Flats (Wilkinson et al, 1987; Gilbert et al, 1993)	Cohort (mortality)	5,952 men (white)	USA
A6.9	Oak Ridge: X-10 and Y-12 plants (Frome et al, 1997) [e]	Cohort (mortality)	28,347 men (white) 1,134 cancer deaths	USA
A6.10	Portsmouth naval shipyard (Silver et al, 2004; Yiin et al, 2005)	Cohort (mortality)	13,468 monitored workers, 2.3% female 24,385 unmonitored workers, 19.5% female	USA
A6.11	Nuclear power industry workers (Howe et al, 2004) [e]	Cohort (mortality)	53,698 monitored workers 11.9% female	USA
A6.12	National Dose Registry of Canada (Ashmore et al, 1998)	Cohort (mortality)	206,620 monitored workers 49% female	Canada

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 40	260,000 [c] (26)	Fuel processing and reactor operation	Recorded exposures to external radiation	35 cause of death groupings including all major cancers
Up to 50	476,146 (25)	Uranium fuel fabrication and uranium hexafluoride production	Recorded exposures to external radiation	46 cause of death groupings including all major cancers
Up to 50	334,473 (26.7)	Uranium fuel fabrication and uranium enrichment processes	Recorded exposures to external radiation	46 cause of death groupings including all major cancers
Up to 40	63,967 (24.3)	Reactor operation	Recorded exposures to external radiation	46 cause of death groupings including all major cancers
Up to 50	n.a.	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All cancers combined, lung*
Up to 32	81,237 (13.6)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	24 cancer groupings and a group of smoking-related cancers
Up to 40	n.a.	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	10 cancer groupings
Up to 45	n.a.	Building, overhauling and repairing nuclear submarines	Recorded exposures to external radiation	Pharynx, oesophagus, pancreas, larynx, lung, kidney, bladder and other urinary organs
1–18	698,051 (13)	Exposures in nuclear fuel cycle	Recorded exposures to external radiation	11 cancer groupings
Up to 36	2,861,093 (14)	Exposures in medicine, dentistry, industry and nuclear power plants	Recorded exposures to external radiation	31 cause of death groupings including all major cancers

The notes to the table are given on p 80

TABLE A2.1 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
A6.13	Atomic Energy of Canada Ltd (Gribbin et al, 1993)[d]	Cohort (mortality)	11,355 monitored workers 24% female	Canada
A6.14	Nuclear power industry workers (Zabotska et al, 2004)[e]	Cohort (mortality)	45,468 monitored workers 17% female	Canada
A6.15	Electricité de France workers (Rogel et al, 2005)[e]	Cohort (mortality)	22,395 monitored workers 3.4% female	France
A6.16	CEA and COGEMA workers (Telle-Lamberton et al, 2007)[e]	Cohort (mortality)	29,204 monitored workers 21.3% female	France
A6.17	Nuclear workers (Engels et al, 2005)[e]	Cohort (mortality)	4,703 monitored workers 2,526 other workers 18% female	Belgium
A6.18	Nuclear workers (Auvinen et al, 2002)[e]	Cohort (incidence)	15,619 monitored workers 5% female	Finland
A6.19	Radiological technologists (Zabel et al, 2006)	Cohort (incidence)	70,859 (who completed two postal questionnaires)	USA

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 30	198,210 (17.5)	Nuclear and reactor research and related technologies	Recorded exposures to external radiation	Pharynx, oesophagus, pancreas, larynx, lung, kidney, bladder and other urinary organs
Up to 38	607,979 (13.4)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All solid cancers combined, buccal cavity and pharynx, oesophagus, colon, rectum*, pancreas, lung, prostate, brain and central nervous system
1–33	258,612 (11.7)	Exposures in nuclear fuel cycle	Recorded exposures to external radiation	All cancers, smoking-related, mouth and pharynx, oesophagus, stomach, colon, liver, pancreas, nasal, larynx, lung, brain and central nervous system, ill-defined
Up to 38	518,718 (17.8)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All cancers combined, mouth and pharynx*, oesophagus*, stomach, liver and gallbladder, pancreas, nasal cavity, larynx, lung, pleura, bone, melanoma of skin, breast (females), uterus and cervix, prostate, bladder, kidney, brain
Up to 25	n.a. (22)	Exposures in nuclear fuel cycle and research	Recorded exposures to external radiation	All cancers combined, stomach, colon, rectal, lung, bladder, renal, brain
Up to 18	130,640 (8.4)	Exposures in nuclear fuel cycle	Recorded exposures to external radiation and annual internal contamination measurement	All cancers combined
n.a.	n.a.	Exposures during medical X-ray procedures	Doses not calculated Details of work practices collected	Thyroid

The notes to the table are given on p 80

TABLE A2.1 ***continued***

Study no.	Study	Type of study	Population studied: Characteristics	Population studied: National origin
HIGH LINEAR ENERGY TRANSFER EXPOSURES				
7	**Cosmic radiation**			
A7.1	European aircraft cockpit crew (Langner et al, 2004)	Cohort (mortality)	19,184 male pilots	Denmark, Finland, Germany, Iceland, Italy, Norway, Sweden
A7.2	European aircraft cabin crew (Zeeb et al, 2003)	Cohort (mortality)	11,079 males 33,063 females	Denmark, Finland, Germany, Greece, Iceland, Italy, Norway, Sweden
A7.3	Nordic airline pilots (Pukkala et al, 2002)	Cohort (incidence)	10,032 males	Denmark, Finland, Iceland, Norway, Sweden

Notes

a An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a statistically significantly higher proportion of the cases were exposed to radiation (case–control studies).

b Cohort included in the National Registry for Radiation Workers (Muirhead et al, 2009).

c Values for monitored workers only.

d Cohort included in the 15-country study of radiation workers in the nuclear industry (Cardis et al, 2005b, 2007; Vrijheid et al, 2007), but with a shorter follow-up.

e Cohort included in the 15-country study of radiation workers in the nuclear industry (Cardis et al, 2005b, 2007; Vrijheid et al, 2007).

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 37	336,413 (17.8)	Cosmic radiation during flight	Calculated from flight hours accrued	All cancers, 'radiation-related cancers', 'cancers not related to radiation', melanoma of the skin
Up to 37	656,465 (15)	Cosmic radiation during flight	Doses not calculated	20 cancer groupings
17 (average)	177,243	Cosmic radiation during flight	Dose calculated based on hours in flight and aircraft-specific average exposures	25 cancer groupings

TABLE A2.2 Strengths and limitations of the less informative epidemiological studies of solid cancers in relation to external radiation exposures (based on UNSCEAR, 2008)

Study no.	Study	Strengths	Limitations
LOW LINEAR ENERGY TRANSFER EXPOSURES			
1	**Exposures to atomic bombings**		
A1.1	Exposure to ionising radiation in adulthood and thyroid cancer incidence (Richardson, 2009)	Long follow-up Histologically derived disease identification for 95% of cases	Few male cases (8) with dose above 0.1 Sv Wide confidence intervals on risk estimates Many cases only received either a very small or zero dose
A1.2	Breast cancer incidence (Land et al, 2003)	See studies 1.1 and 1.2 in Table 2.2	Older dosimetry (DS86) used For other points see studies 1.1 and 1.2
2	**Treatment of malignant disease**		
2.2	**Adult exposures**		
A2.2.1	Soft tissue and bone sarcoma following breast cancer (Rubino et al, 2005)	Analyses based on dose received at the site of sarcoma	Small number of cases Mostly high doses
A2.2.2	Lung cancer following Hodgkin disease (van Leeuwen et al, 1995)	Individual estimates of radiation dose to the area of the lung where the tumour developed Individual data on smoking habits Extensive data on doses from chemotherapy	Small number of cases Limited follow-up (median 10 years) Few females
A2.2.3	Breast cancer following Hodgkin disease (van Leeuwen et al, 2003)	Individual estimates of radiation dose to the area of the breast where the tumour developed Individual data on smoking habits Extensive data on doses from chemotherapy	Small number of cases Mostly high doses

TABLE A2.2 ***continued***

Study no.	Study	Strengths	Limitations
6	**Occupational exposures**		
A6.1–A6.18	Nuclear workers (Wilkinson et al, 1987; Beral et al, 1988; Fraser et al, 1993; Gilbert et al, 1993; Gribbin et al, 1993; Carpenter et al, 1994; Douglas et al, 1994; Frome et al, 1997; Ashmore et al, 1998; McGeoghegan and Binks, 2000a,b, 2001; Auvinen et al, 2002; Howe et al, 2004; Atkinson et al, 2004, 2007; Silver et al, 2004; Zabotska et al, 2004; Engels et al, 2005; Rogel et al, 2005; Yiin et al, 2005; Wing and Richardson, 2005; Telle-Lamberton et al, 2007)	Personal dosimetry Low dose protracted and multiple exposures	Mostly relatively small cohorts, many of which are contained in larger cohorts included in Table 2.2 Low doses make demonstration of radiation effect difficult in small studies Possible confounding effect of chemicals and other agents in the workplace Healthy worker effect Mortality follow-up for many studies Lifestyle factors (eg smoking histories) generally not available
A6.19	Radiological technologists (Zabel et al, 2006)	Large cohort	No dosimetry
HIGH LINEAR ENERGY TRANSFER EXPOSURES			
7	**Cosmic radiation**		
A7.1–A7.3	Aircrew studies (Pukkala et al, 2002; Zeeb et al, 2003; Langner et al, 2004)	Response to neutrons as well as gamma radiation	Complex dosimetry Low doses make demonstration of radiation effect difficult

TABLE A2.3 Less informative epidemiological studies of solid cancers in relation to internal radiation exposures (based on UNSCEAR, 2008)

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
LOW LINEAR ENERGY TRANSFER EXPOSURES				
8	**Medical exposures**			
A8.1	Iodine-131 thyroid cancer therapy (Hall et al, 1991)[b]	Cohort (incidence)	834 exposed persons 1,121 unexposed persons 75% female Age: 5–75 (mean 48)	Sweden
A8.2	Iodine-131 thyroid cancer therapy (de Vathaire et al, 1997)[b]	Cohort (incidence)	846 persons with therapeutic exposures 501 persons with diagnostic exposures 274 unexposed persons 79% female Age: 5–89 (mean 40)	France
A8.3	Iodine-131 thyroid cancer therapy (Dottorini et al, 1995)[b]	Cohort (incidence)	730 exposed persons 201 unexposed persons 75% female Age: 0–45	Italy
9	**Enironmental exposures**			
A9.1	Marshall Islands fallout (Takahashi et al, 2003)	Cohort (incidence)	3,709 exposed persons	Marshall Islands
HIGH LINEAR ENERGY TRANSFER EXPOSURES				
12	**Diagnostic examinations**			
A12.1	Early Thorotrast patients (Mori et al, 1999a,b)	Cohort (mortality)	262 exposed persons 1,630 unexposed persons Age: 20–39	Japan
A12.2	Later Thorotrast patients (Kido et al, 1999; Mori et al, 1999b)	Cohort (mortality)	150 exposed persons Age: 15–39	Japan
13.3	**Occupational exposure: various**			
A13.3.1	Mound facility (Wiggs et al, 1991)	Cohort (mortality)	4,402 males (white)	USA

Table A2.3 extends on to the facing page and continues for three pairs of pages

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
2–34	25,830 (13.2)	Treatment of thyroid cancer	Individual values of activity administered	Salivary glands*, kidney*, all other sites
2–37	14,615 (9.0)	Diagnostic and therapeutic iodine-131 exposures for thyroid cancer	Individual values of activity administered and organ dose estimates	Colon, all other sites
0–80	n.a.	Iodine-131 therapy for differentiated thyroid cancer	Individual values of activity administered	Salivary glands, head and neck, stomach, colorectal, lung, melanoma of skin, bladder, neuroendocrine
>40	n.a.	Fallout from nuclear weapons tests	Short-lived radionuclides from nuclear explosion	Thyroid
18–68	n.a.	Injection with Thorotrast	Amount injected	Liver*, lung, bone sarcoma
34–65	n.a.	Injection with Thorotrast	Amount injected	Liver*, lung
Up to 40	104,326 (23.7)	Exposures in nuclear fuel cycle and research	Measurement of polonium in urine	All cancers combined, oral, digestive, lung, bone, skin, prostate, bladder kidney, brain, thyroid

The notes to the table are given on p 88

TABLE A2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
A13.3.2	Fernald (Ritz, 1999)	Cohort (mortality)	4,014 males (white) Age at entry: 30.4 (average)	USA
A13.3.3	Rocketdyne/Atomics International (Ritz et al, 2000; Boice et al, 2006)	Cohort (mortality)	5,743 workers 8% female	USA
A13.3.4	Florida phosphate workers (Checkoway et al, 1996)	Cohort (mortality)	17,929 male workers Age at entry: median 25	USA
A13.3.5	Iron and steel workers (Lili et al, 1994)	Cohort (mortality)	Males 5,985 exposed 2,849 unexposed	China
13.4	**Occupational exposure: radon**			
A13.4.1	Uranium miners: nested case–control study (Leuraud et al, 2007)	Nested case–control (mortality)	62 cases 320 controls	France

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 49	124,177 (30.9)	Exposures in nuclear fuel cycle and research	Measurement of uranium, thorium and radium compounds in urine, plus environmental area sampling Recorded exposures to external radiation	Lung, respiratory tract, upper GI tract, lower GI tract, bladder and kidney
Up to 51	161,605	Exposures in nuclear research and development	Measurement of uranium, mixed-fission products, strontium, caesium and plutonium in urine and faeces, plus *in vivo* whole-body and lung counts Recorded exposures to external radiation	20 individual cancer groupings, smoking-related cancers
Up to 44	545,867 (23.7)	Exposure to mining and chemical processing of phosphate ores	Assessments of cumulative exposures to alpha and gamma radiation based on job histories	Lung
Up to 17	111,286 (12.6)	Exposure to dust containing thorium in an iron and steel company	Assessment of lung doses from inhalation	Lung
n.a.	n.a.	Exposure to radon during underground uranium mining	Annual WLM of exposure estimated from ambient measurements and detailed occupational history (estimated retrospectively for period prior to 1956)	Lung

The notes to the table are given on p 88

TABLE A2.3 ***continued***

			Population studied	
Study no.	**Study**	**Type of study**	**Characteristics**	**National origin**
A13.4.2	Uranium miners: cohort study (Laurier et al, 2004)	Cohort (mortality)	1,785 miners	France
A13.4.3	Cornish tin miners (Hodgson and Jones, 1990)	Cohort (mortality)	1,758 miners	UK

Notes

a An asterisk denotes sites for which statistically significant excesses are reported in the exposed group (cohort studies) or for which a statistically significantly higher proportion of the cases were exposed to radiation (case–control studies).

b Cohort included in study 8.5 in Table 2.3 (Rubino et al, 2003).

Period of follow-up following exposure (or first exposure) (years)	Total person years (mean duration of follow-up per person)	Type of exposure	Type of dosimetry	Cancers studied [a]
Up to 48	56,572 (31.6)	Exposure to radon during underground uranium mining	Annual WLM of exposure estimated from ambient measurements and detailed occupational history (estimated retrospectively for period prior to 1956)	Buccal cavity, oesophagus, stomach, small intestine (including colon and rectum), Liver, pancreas, gall bladder, larynx, lung, bone, bladder and kidney, brain and central nervous system
Up to 43	66,900 (26.4)	Exposure to radon decay products	Measurements in mines from 1967 used to estimate doses; for previous years extrapolation was used	Lung, stomach All non-lung cancers combined and 28 individual cancer categories included in study 13.4.2 in Table 2.3, as part of the pooled analysis by Darby et al (1995)

TABLE A2.4 Strengths and limitations of the less informative epidemiological studies of solid cancers in relation to internal radiation exposures (based on UNSCEAR, 2008)

Study no.	Study	Strengths	Limitations
LOW LINEAR ENERGY TRANSFER EXPOSURES			
8	**Medical exposures**		
A8.1–A8.3	Iodine-131 thyroid cancer therapy patients (Hall et al, 1991; Dottorini et al, 1995; de Vathaire et al, 1997)	Incidence follow-up Administered activities of iodine-131 known Unexposed group Exclusion of patients who received external radiotherapy in study A8.2	Individual doses not computed Small numbers for specific cancer types Few patients irradiated at young ages Possibility of selection bias by treatment
A9.1	Marshall Islands fallout (Takahashi et al, 2003)	Control group includes *in utero* subgroup	Age-at-exposure and attained-age effects inseparable Possible exposure misclassification
HIGH LINEAR ENERGY TRANSFER EXPOSURES			
12	**Treatment of benign disease**		
A12.1, A12.2	Thorotrast patients (Kido et al, 1999; Mori et al, 1999a,b)	Unexposed comparison group	Small cohorts Chemical attributes of Thorotrast might influence risks
13	**Occupational exposures**		
A13.3.1–A13.3.3	Nuclear workers (Wiggs et al, 1991; Ritz, 1999; Ritz et al, 2000; Boice et al, 2006)	Individual measurements of radionuclides	Small cohorts
A13.3.4	Florida phosphate workers (Checkoway et al, 1996)	Relatively large number of person-years Assessment of exposures to other agents (eg silica and acid mists)	Not possible to obtain direct quantitative estimates of exposure levels Absence of data on smoking habits for lung cancer analysis
A13.3.5	Iron and steel workers (Lili et al, 1994)	Assessments made of lung doses from inhalation of thorium Information available on smoking habits	Lung doses generally low Small number of deaths for specific cancer types
A13.4.1	Uranium miners: nested case–control study (Leuraud et al, 2007)	Information collected on individual smoking habits Radon exposures relatively well characterised	Limited smoking information (generally ever/never) Fairly small number of cases
A13.4.2	Uranium miners: cohort study (Laurier et al, 2004)	Increased power over previous analyses	No smoking information Small numbers of deaths for specific cancers
A13.4.3	Cornish tin miners (Hodgson and Jones, 1990)	Protracted exposures over several years	Poor dosimetry: early doses estimated by extrapolation Individual doses based on job histories

3 Results of Epidemiological Studies

3.1 Introduction

In this chapter, brief background information will be given on the causes of a range of cancers. Results from epidemiological studies of groups exposed to ionising radiation will then be reviewed, grouped according to the type of exposure, ie whether exposure was predominantly external or internal, or to low or high linear energy transfer (LET) radiation, although recognising that some studies do not fall simply into a single category. As well as the studies listed in Tables 2.1–2.4 that involve individual estimates of radiation exposure, reference will sometimes be made to studies (eg of radiotherapy patients) where it is known only whether someone was irradiated or not, in instances where the latter studies provide additional information. Conclusions will then be drawn concerning the strength of evidence for an association with radiation exposure and on the extent to which radiation risks might be modified by other factors.

The cancers are defined according to the International Classification of Diseases (ICD), which groups neoplasms mainly by primary site. In general, the discussion of a specific cancer includes malignancies of any histological type arising in the relevant site. The exceptions are mesothelioma, Kaposi sarcoma and all types of leukaemia and lymphoma. All of these have their own codes in the ICD; furthermore, leukaemias and lymphomas are outside the scope of this report. Also, melanoma of skin and non-melanoma skin cancer form different categories in the ICD, and are considered separately here.

The tables below aim to summarise risks within various studies using measures of relative risk and, where available, absolute risk. These estimates are mainly based on fitting models under which either the relative or the absolute risk varies as a *linear* function of radiation dose. In particular, the relative risk model is of the form:

$$RR = 1 + (ERR \times D)$$

where RR is the relative risk, D is the radiation dose, and ERR is the excess relative risk per unit radiation dose.

Thus a value of ERR greater than zero indicates that the relative risk increases with increasing dose, a value of ERR less than zero indicates that the relative risk decreases with increasing dose, whilst an estimated value of ERR close to or equal to zero would correspond to no strong evidence of a trend in the relative risk with dose. Based on a model for the relative risk, the absolute cancer rate (see AR below) can be derived by multiplying the relative risk by the cancer rate in an unexposed comparison group (see BR below).

This linear model should be contrasted with the log-linear model that is commonly used in analyses of epidemiological data. Under this latter model, the logarithm of the relative risk is modelled to vary as a

linear function of explanatory variables such as radiation dose. This model has been favoured in the analysis of cohort data and the related logistic model is commonly used in analysing case–control data because the statistical properties of the parameter estimates are well understood and because it is relatively simple to fit these models (McCullagh and Nelder, 1989). However, radiobiological considerations (see ICRP, 2005) and – as will be described later – some key epidemiological findings would tend to favour a model under which the radiation risk varies as a linear function of radiation dose, rather than as an exponential function of dose, as would be implied under a log-linear model. Furthermore, software exists that allows models such as the linear model to be fitted to cohort or case–control data – for example, the Epicure package (Preston et al, 1993).

The corresponding linear model based on the absolute risk takes the form:

$$AR = BR + (EAR \times D)$$

where AR is the absolute cancer rate in the exposed population (expressed in this report as the number of cancers per 10,000 persons per year), BR is the baseline cancer rate, ie the rate that would be expected to arise in the absence of radiation exposure, D is the radiation dose, and EAR is the excess absolute risk per unit radiation dose.

Thus a value of EAR greater than zero indicates that the absolute risk increases with increasing dose, a value of EAR less than zero indicates that the absolute risk decreases with increasing dose, whilst a value of EAR equal to zero would correspond to no trend in the absolute risk with dose.

As an example, if the EAR were estimated to be 2 cases per 10,000 persons per year per sievert (Sv) and the baseline rate BR were 4 cases per 10,000 persons per year, then the absolute rate in a population that receives a dose (D) of 1 Sv would be

$$AR = 4 + (2 \times 1) = 6 \text{ cases per } 10{,}000 \text{ persons per year}$$

In this simple example, the corresponding relative risk at 1 Sv would be

$$RR = AR/(BR \times D) = 6/4 = 1.5$$

and the excess relative risk at 1 Sv would be

$$ERR = RR - 1 = 0.5$$

In practice, the link between estimates of EAR and ERR would not be as simple as in this example, because the study population would contain people of different ages with different cancer rates. Fitting the above models therefore needs to take account of age and other factors such as sex and time that influence cancer rates (Breslow and Day, 1980, 1987). For the most part, the estimates of ERR and EAR given in the following tables are the values reported by the study authors, often based on the authors' own standardisation for factors such as age and sex. Ideally the same method of standardisation would have been used for all of the ERR and EAR estimates presented in this chapter. However, this was not feasible because the detailed data needed to apply such a standardisation were generally not available. Consequently, the approach taken has been to list ERR and EAR estimates grouped by factors such as age or sex in instances where such values have been reported and to highlight those populations that – for example – were exposed in childhood only.

The ERR and EAR are not the only means by which a raised risk can be characterised. Another quantity is the population attributable risk, sometimes shortened to attributable risk. This quantifies the reduction in the number of cancers in a population that would be expected if the exposure was removed. A term with a similar meaning is the 'aetiological fraction'. This is defined as the proportion of cases in which the exposure is directly responsible for disease. This measure is not always simple to interpret as a particular agent may be responsible for increasing the risk of a number of different cancers, raising the possibility that the proportion of cancers attributable to a particular agent may add up to more than 100%. It should also be noted that all excess cases are aetiological cases but the reciprocal statement is not true. Attributable risks will not be considered in this chapter but will be addressed later in this report when considering the numbers of cases of solid cancer that may be attributed to radiation exposure.

In some instances, estimates of risk have been derived using a model that takes account of a decrease in the risk per unit dose at very high doses, which may reflect the effect of cell killing. Such levelling-off or even decreases in the dose–response relationship have been seen in some studies of patients treated with radiotherapy for a first cancer, where the doses to organs in which a second cancer might subsequently develop were perhaps of the order of several tens of sievert. Consequently, estimates of the ERR at 1 Sv are cited in the tables below, rather than the ERR Sv^{-1}.

The Life Span Study cohort of Japanese atomic bomb survivors throughout the tables is assigned to the category of 'external low linear energy transfer exposures'. Of the dose received by the survivors, 1–2% was due to neutrons, most of the rest being due to high energy (mostly 2–5 MeV) gamma radiation (Roesch, 1987; Young and Kerr, 2005). Even after application of a neutron RBE of 10 (as is done in most of the analysis presented here), the dose in this cohort is predominantly external low LET. Similar simplifications are made for various other studies. For all solid cancers combined (Table 3.24), the Techa River cohort (Krestinina et al, 2005, 2007) is assigned to the category of 'external low LET exposures', since 75% of the stomach dose is thought to be from this source (with most of the rest from caesium-137). In contrast, in relation to leukaemia, 92% of the bone marrow dose is thought to be from internal beta emitters (Krestinina et al, 2005).

3.2 Oral Cavity

3.2.1 General epidemiology

There are around 4,500 diagnoses of, and 1,500 deaths from, oral/oropharyngeal cancer annually in the UK, making it a relatively uncommon cancer (Cancer Research UK, 2008). Although age-standardised incidence rates in males have increased from 7 per 100,000 in 1975 to 10 per 100,000 in 2003, and the corresponding rates in females from 3 per 100,000 in 1975 to 4 per 100,000 in 2003, these increases are confined to those younger than age 70 years. In older age groups the rates have been decreasing. Patterns in mortality have been similar. Cancer of the salivary glands is a relatively rare form of oral cancer with age-standardised incidence rates of about 0.5 per 100,000 people in the UK per year (Parkin et al, 2006). More than 90% of oral malignancies are squamous cell carcinomas (Daley and Darling, 2003). Tobacco smoking, excess alcohol consumption and their combined effects are the main established causes of oral/oropharyngeal cancers in the UK (Cancer Research UK, 2008).

3.2.2 Findings from studies of radiation exposure

3.2.2.1 Informative studies and evidence for association and causality

Table 3.1 summarises findings from cohort and case–control studies of salivary gland cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. Many of these studies have only analysed malignant and benign cancers together, where this is the case the number of benign cases has been stated. As well as these studies, information is available from studies that lack individual assessments – for example, the studies by Preston-Martin et al (1988), Dietz et al (1993) and Horn-Ross et al (1997), of salivary gland tumours in patients who had multiple dental X-rays.

Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the most informative studies regarding radiation exposure are the Life Span Study and the study of patients who received tonsil irradiation. Because it is an uncommon group of cancers, the studies suffer from lack of precision. Dosimetry for dental X-rays is uncertain and there may therefore be recall bias in the retrospective studies of diagnostic X-rays (Berrington de González et al, 2003).

Based on the epidemiological evidence from the studies listed in Table 3.1 and the other studies mentioned above, it can be concluded that there is *suggestive* evidence of an association between radiation exposure and cancers of the salivary glands. Furthermore, taking account of the dose–response relationship found it can be concluded that this association is *probably* causal. It is unclear whether other types of oral/oropharyngeal cancers are associated with radiation exposure.

3.2.2.2 Estimates of radiation risks

The Life Span Study indicates that rates of salivary gland cancer increase with increasing level of radiation dose. At lower doses, there is also evidence of possible raised risks from the study of multiple dental X-rays.

For external radiation, the best estimate of risk in relation to radiation exposure is that given by Preston et al (2007) based on analysis of the Life Span Study cohort, namely an ERR of 1.80 (95% confidence interval (CI) 0.6, 4.0).

There is no evidence about the effects of internal radiation exposure.

3.2.2.3 Modifying factors

In the Life Span Study there is evidence that the risk of radiation-induced salivary gland tumours decreases with age at exposure or attained age, but there is no difference in the magnitude of the risk between males and females. There is no information on how radiation risks might be modified by exposures to agents other than radiation.

3.2.2.4 Gaps in knowledge

There is little information on the effect of radiation exposure and oral/oropharyngeal cancers other than those of the salivary gland. There is no information on the potential modifying factors for the relationship with cancers of the salivary gland (see above).

TABLE 3.1 Risk estimates for salivary gland cancer incidence and mortality from studies of radiation exposure

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Gy or more (weighted skin dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 95% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	23	n.a. [a]	~0.2	1,165,788	1.8 (0.6, 4.0) [b]	n.a.
1.1	Life Span Study, 1950–87 (Land et al, 1996)	31	n.a.	~0.2	2,539,101	4.47 (2.45, 8.46)	n.a.
3.1.1	Childhood X-ray treatment for Tinea Capitis (Shore et al, 2003)	6 (4 benign)	n.a.	n.a.	n.a.	1.8 (0.4, 8.9)	n.a.
3.1.4	Tonsil irradiation (Schneider et al, 1998)	89 (67 benign)	n.a.	4.2	n.a.	0.82 (0.04, infinity)	n.a.
Mortality							
4.7	Medical and dental radiography of the head (Preston-Martin et al, 1988)	408 (269 benign)	n.a.	0.19	n.a.	1.5 [c] (0.68, 3.41)	n.a.
6.3	Nuclear workers in Japan (Iwasaki et al, 2003) [d]	24	26.7	0.0153	~540,000	*Oral cancer* 1.34 [e] (0.28, 3.92)	n.a.
8.2	Thyroid cancer patients treated with iodine-131 (Hall et al, 1991)	3	n.a.	n.a.	10,073	15 (3.09, 43.84)	n.a.

Notes

a Not available.
b 90% CI here.
c Relative risk at 0.1 Sv.
d The values given here are based on the 119,484 workers who were followed up prospectively.
e Relative risk for 20–50 mSv cumulative dose group.

3.3 Oesophagus

3.3.1 General epidemiology

Oesophageal cancer varies widely by country and ethnic group (Munoz and Day, 1996; Chang-Claude et al, 1997), with low rates in many countries but extremely high rates among Chinese and certain central Asian groups and intermediate rates in black populations (Munoz and Day, 1996). For example, age-standardised rates of 183.8 and 123.1 cases per 100,000 persons for males and females, respectively, have been observed in parts of China (Parkin et al, 2002), whereas the rates are fewer than 10 cases per 100,000 persons (Parkin et al, 2002) in many European countries. In the UK, incidence rates in 2004 were 14.1 and 5.5 cases per 100,000 persons for males and females, respectively, and in 2005 mortality rates of 13.4 and 4.9 deaths per 100,000 persons for males and females, respectively, were recorded (Cancer Research UK, 2008).

Since oesophageal cancer is generally fatal, mortality rate is a good surrogate for incidence. There are two major types of oesophageal cancer, squamous cell carcinoma and adenocarcinoma. Squamous cell cancer arises from the cells that line the upper part of the oesophagus. Adenocarcinoma arises from glandular cells that are present at the junction of the oesophagus and stomach, and is often associated with gastrointestinal reflux and Barrett's oesophagus. The major known risk factors for oesophageal cancer are heavy alcohol consumption, tobacco use and chewing of betel nut (Munoz and Day, 1996). There are indications of familial aggregation among cases in certain areas of China, which implies that heritable genetic factors may account for part of the high risk observed in these areas, although the pairwise association between parents but not between siblings indicates that environmental factors play a stronger role after childhood (Chang-Claude et al, 1997). Other possible risk factors, for which the weight of evidence is less strong, are consumption of pickled foods and nutritional deficiency (Munoz and Day, 1996).

3.3.2 Findings from studies of radiation exposure

3.3.2.1 Informative studies and evidence for association and causality

Table 3.2 summarises findings from cohort studies of radiation-exposed populations for which individual dose estimates are available. Based on the evidence presented, there is suggestive evidence of an association with radiation exposure. Cancer incidence data from the Life Span Study, which began just over 12 years after exposure, shows a significant excess risk of oesophageal cancer based on follow-up to 1998 (Preston et al, 2007). The Life Span Study mortality data also show evidence of excess risk (Preston et al, 2003) (Table 3.2).

Oesophageal cancer data were available from several worker studies following high LET exposures. In a study of three groups of workers exposed to plutonium in three UK nuclear industry workforces, no clear excess of oesophageal cancer was seen (see Table 3.2), nor was any excess seen among workers monitored for exposures to radionuclides of uranium, polonium and actinium and to other radionuclides (apart from tritium) (9 observed versus 16.1 expected deaths), although doses to the oesophagus were probably small (Carpenter et al, 1998).

There are few data on internal low LET exposures and oesophageal cancer. A study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan (Bauer et al, 2005) reported a highly statistically significant trend of increasing risk with dose in females ($p = 0.003$), although not for males ($p = 0.46$). The aggregate ERR based on an internal analysis was 2.37 Sv^{-1} (95% CI 1.47, 3.63); however, when analysis was restricted to the exposed group, based on individual dose estimates, the trend estimate was much reduced, and no longer statistically significant, 0.18 Sv^{-1} (95% CI −0.09, 0.66). However, ecological bias may operate in this study, so these findings should be treated with caution. Data from patients treated with iodine-131 for adult hyperthyroidism (Ron et al, 1998) showed no increased risk of this cancer, but the doses to the oesophagus were small.

Several studies of workers exposed to external radiation have reported data on the risks of oesophageal cancer (Table 3.2). Of these, three studies reported data based on internal dose–response comparisons. The UK National Registry for Radiation Workers (Muirhead et al, 2009) reported a dose–response association that was non-significant, based on 186 cases of oesophageal cancer in informative strata (strata defined by age group, sex, interval of follow-up, etc, with at least one cancer death and at least two dose groups with persons contributing to the follow-up) and a mean dose of 0.024 Sv. A smaller US study of Los Alamos workers (Wiggs et al, 1994) reported a marginally positive dose response ($p < 0.1$), but a deficit compared to the US population (22 observed versus 27.4 expected). A study of oesophageal cancer incidence among workers in the Canadian National Dose Registry (Sont et al, 2001) reported a null dose–response association based on 22 observed cancers, and an update of the segment of the Registry concerning nuclear power industry workers also produced a null result (Zablotska et al, 2004).

Other studies of workers – US Oak Ridge workers (Frome et al, 1990), radiation workers at Électricité de France (Rogel et al, 2005), Japanese nuclear workers (Iwasaki et al, 2003) and radiological technologists (radiographers) in Japan and the USA (Mohan et al, 2003; Yoshinaga et al, 2004) – reported deficits in oesophageal cancer mortality rates based on comparisons with reference general populations. Only the study of Chinese medical X-ray workers reported an excess of oesophageal cancer among both early workers (mean dose of 0.55 Sv) and more recent workers (0.08 Sv) (Wang et al, 2002). It is notable that the workers in this study had higher radiation exposures than those in the other studies, and this, possibly combined with the higher baseline incidence in this population, increases the statistical power to observe excess cases. In a UK study of Springfields uranium workers (McGeoghegan and Binks, 2000a), no excess of oesophageal cancer was seen (25 observed versus 34.54 expected) (Table 3.2).

The ankylosing spondylitis study was the only study of medically exposed populations to report a significant risk of radiation-associated oesophageal cancer (Weiss et al, 1994). A study of US females treated with radiation for primary breast cancer documented relative risks of 2.83 (95% CI 1.35, 5.92) and 2.17 (95% CI 1.67, 4.02) for squamous cell oesophageal cancer occurring between 5 and 9 years and at 10 or more years, respectively, following radiotherapy (Zablotska et al, 2005). This increase was mainly due to tumours located in the upper and middle thirds of the oesophagus. No assessment of radiation doses has been carried out for this cohort.

TABLE 3.2 Risk estimates for oesophageal cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted stomach dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	152	n.a. [a]	0.21	1,165,788	0.52 (0.15, 1.0)	0.58 (0.18, 1.1)
2.2.1	Cervical cancer cohort (Boice et al, 1985) [b]	12	11.0	0.35	178,243	0.26 (−1.1, 1.3) [c]	0.16 (−0.6, 1.3) [c]
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	300	n.a.	0.025	2,388,848	0.154 (−0.79, 1.68)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	130	n.a.	0.19	n.a.	0.61 (0.15, 1.2)	1.1 (0.28, 2.0)
	Females	44	n.a.	0.18	n.a.	1.7 (0.46, 3.8)	0.51 (0.15, 0.92)
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994)	9	9.27 [d]	0.05	47,144	−0.58 (<−0.2, 13.9)	n.a.
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [e]	74	38 [d]	5.55	287,095	0.17 [f] (0.09, 0.25) [c]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	144	n.a.	0.0194	5,192,710	<0 (90% CI n.a.)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	341	n.a.	0.025	2,433,573	0.146 (−0.72, 1.42)	n.a.

TABLE 3.2 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES						
Mortality						
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	317 [g]	n.a.	0.634 [h]	284,260	0.18 (−0.09, 0.66) [i]
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Mortality						
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	23	21.3 [d]	n.a.	n.a.	0.81 (0.46, 1.39) [j]

Notes
a Not available.
b The values given exclude the period within 10 years of treatment.
c 95% CI here.
d Based on national mortality rates.
e The values given exclude the period within 5 years of first treatment.
f Dose–response analysis based on the number of treatment courses given.
g Number of cancers in both the exposed and the comparison group.
h Average cumulative dose in the exposed group, arising from internal and external exposures.
i Based on a dose–response analysis conducted solely within the exposed group.
j Relative to workers not monitored for any radionuclide.

3.3.2.2 Estimates of radiation risks

The ERR of oesophageal cancer in the latest Life Span Study incidence data (Preston et al, 2007) is 0.52 Sv^{-1} (90% CI 0.15, 1.0); the corresponding EAR is 0.58 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.18, 1.1). In the latest Life Span Study mortality data (Preston et al, 2003) the ERR for males is 0.61 Sv^{-1} (90% CI 0.15, 1.2) and for females is 1.7 Sv^{-1} (90% CI 0.46, 3.8); the corresponding EAR for males is 1.1 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.28, 2.0) and for females is 0.51 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.15, 0.92). There is a single estimate of radiation risk from internal low LET exposure, from the Semipalatinsk study of Bauer et al (2005), and an ERR of 0.18 Sv^{-1} (95% CI −0.09, 0.66) (Table 3.2). Risk estimates for other exposed groups are given in Table 3.2.

3.3.2.3 Modifying factors

There are no statistically significant variations in oesophageal cancer ERR or EAR by age at exposure, time since exposure or attained age in the latest Life Span Study incidence data (Preston et al, 2007).

3.3.2.4 Gaps in knowledge

There is no information on risks from internal high LET radiation, and only a single study on risks from internal low LET radiation exposure. It is likely that oesophageal cancer displays similar variations in relative risk as other solid cancers in relation to age at exposure and attained age, but the available data lack the statistical power to indicate such trends.

3.4 Stomach

3.4.1 General epidemiology

Stomach cancer is the fourth most common malignancy worldwide and appears to be the second leading form of fatal cancer (Nomura, 1996; Stewart and Kleihues, 2003). Rates are higher among males than females and show a sharp increase with age. The incidence of stomach cancer varies considerably with geographical location and among different ethnic groups within the same locality (Stewart and Kleihues, 2003). Approximately 60% of all stomach cancers occur in developing countries. The highest rates are found in Eastern Asia, the Andean regions of South America, and Eastern Europe, while low rates are found in North America, Northern Europe and most countries in Africa and Southeast Asia (Parkin et al, 2002; Stewart and Kleihues, 2003). For example, annual age-standardised rates of 145.0 and 34.5 cases per 100,000 persons for males and females, respectively, have been observed in parts of China (Parkin et al, 2002), whereas in many European countries the rates are fewer than 30 cases per 100,000 persons (Parkin et al, 2002). In the UK, incidence rates in 2004 were 14.3 and 6.1 cases per 100,000 persons for males and females, respectively, and in 2005 mortality rates of 9.4 and 4.0 deaths per 100,000 persons for males and females, respectively, were recorded (Cancer Research UK, 2008).

Studies of migrants suggest that environmental factors may be largely responsible for the variation in rates (Nomura, 1996). Of particular interest is the fact that Japanese people have had much higher rates of stomach cancer than those in Western countries. In most countries, including Japan, stomach cancer incidence and mortality rates have declined markedly over the past 50 years (Nomura, 1996; Stewart and Kleihues, 2003). These changes are likely to reflect changes in diet, including increased consumption of fresh vegetables and fruit and decreased salt intake which case–control studies have shown to be linked to reduced stomach cancer risks (Kono and Hirohata, 1996). Dietary factors are important, and infection with *Helicobacter pylori* (Sack et al, 1997; Forman and Burley, 2006), especially with certain genetic or physiological co-factors, has been associated with elevated risks of stomach cancer (Correa and Chen, 1994; Kono and Hirohata, 1996).

3.4.2 Findings from studies of radiation exposure

3.4.2.1 Informative studies and evidence for association and causality

Based on the results presented in Table 3.3, there is evidence of an association with radiation exposure. A summary of results from studies in relation to external low LET exposure is shown in Table 3.3. The dose response seen in the Life Span Study incidence data up to 1998 (Preston et al, 2007) was consistent with linearity, and the excess relative risk per sievert (ERR Sv^{-1}) was higher (by a factor of 2.3) for females than for males, decreased (but not significantly) with increasing age at exposure, and decreased (significantly) also with attained age, even after adjustment for age at exposure. The findings for mortality to 1997 (Preston et al, 2003) were similar; 1,685 stomach cancer deaths occurred among those people who received doses of at least 5 mSv. Of these, it was estimated that about 100 were attributable to the radiation exposure (Preston et al, 2003). The ERR Sv^{-1} was greater for females (0.65) than for males (0.20), as was the excess absolute risk (EAR) per 10^4 PY Sv (3.3 and 2.1, respectively). For the ERR, the

patterns of variation of radiation effects with age at exposure and attained age were not significantly different from those for solid tumours as a whole. Specifically, the ERR Sv^{-1} declined substantially with increasing age at exposure, but declined very little with increasing attained age. For the EAR, there was no significant increase or decrease with age at exposure, a pattern that differed from that for all solid cancers combined. The EAR showed a steep increase with attained age, similar to that for all solid cancers as a group (Preston et al, 2003). The difference in the patterns for the ERR and EAR with age at exposure is related to the decline in baseline rates with birth cohort, a variable that is confounded with age at exposure.

The major studies of patients whose stomachs were irradiated with reasonably high doses — particularly the studies of patients treated for cervical cancer (Boice et al, 1985, 1988), ankylosing spondylitis (Weiss et al, 1994) and peptic ulcer (Griem et al, 1994; Carr et al, 2002) — produced estimates for EAR Sv^{-1} that were appreciably smaller than those from the Life Span Study, but the ERR estimates of these studies and of the Life Span Study were statistically compatible. The latest update of the US peptic ulcer study (Carr et al, 2002) reported as its main result an excess relative risk per gray (ERR Gy^{-1}) of 0.06 (95% CI 0.02, 0.10) based on persons with 10 or more years of follow-up. However, among patients treated with 1–10 Gy, the ERR Gy^{-1} was somewhat higher, 0.20 (95% CI 0.0, 0.73). This estimate should be treated with caution, however, as the numbers of deaths were relatively small (47 stomach cancer deaths among 1,941 patients, or for the 1–10 Gy group 11 deaths among 309 patients), the mean dose in that group was high (14.8 Gy overall, 8.9 Gy among the 1–10 Gy group), and the patients were being treated for a stomach condition that may cause hyperplasia or other cellular responses that potentially could alter carcinogenic susceptibility. The irradiated patients were predominantly male (78%), and a quarter had a history of stomach surgery. The *H. pylori* status of the patients was not known. The ERR Gy^{-1} estimates in the lower dose group are compatible with those based on male survivors of the atomic bombings; the EAR was not evaluated.

Several studies of occupational radiation exposure have reported data on stomach cancer incidence or mortality. Most studies, including the 15-country (Cardis et al, 2007), UK NRRW (Muirhead et al, 1999, 2009) and Canadian National Dose Registry (Ashmore et al, 1998) studies, provide little evidence of a dose–response relationship for stomach cancer, but this may be due to the low doses and limited statistical power. A recent study of US nuclear power industry workers (Howe et al, 2004) indicated a large but non-significant ERR Gy^{-1} based on 16 deaths. In a study of Japanese nuclear industry workers (Iwasaki et al, 2003), the risk of stomach cancer was not elevated in comparison with the general population, but the dose response based on 428 deaths was statistically significant; however, the finding was no longer significant when a Bonferroni procedure was applied to take account of the multiple statistical tests that were performed. The authors noted the possibility of confounding by dietary factors and socioeconomic factors. The study of Artalejo et al (1997) reported a slight deficit of stomach tumour mortality among workers for the Spanish Nuclear Energy Board; the standardised mortality ratio (SMR) was 0.81 (95% CI 0.49, 1.26) but was based on only 19 cancer deaths, of which 7 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation.

There have been two relevant studies of occupational exposure in medicine more recently reported, in the USA (Mohan et al, 2002; Sigurdson et al, 2003) and in China (Wang et al, 2002); in neither study have individual dose estimates been derived, so their utility for quantitatively understanding radiation risks is

TABLE 3.3 Risk estimates for stomach cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted stomach dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	1,084	n.a. [a]	0.22	436,180	0.21 (0.10, 0.34) [b]	9.4 (4.4, 16) [b]
	Females	1,011	n.a.	0.21	729,608	0.47 (0.29, 0.68) [b]	9.7 (6.4, 14) [b]
	Both sexes						
	Age at exposure <20 y	435	n.a.	0.22	586,255	0.44 (0.20, 0.83) [c]	9.9 (4.5, 18) [c]
	20–39 y	809	n.a.	0.21	378,204	0.34 (0.22, 0.47) [b]	9.5 (6.1, 14) [b]
	40+ y	851	n.a.	0.20	201,330	0.25 (0.12, 0.44) [d]	9.2 (4.2, 16) [c]
	All	2,095	n.a.	0.21	1,165,787	0.34 (0.22, 0.47) [b]	9.5 (6.1, 14) [b]
2.2.3	Cervical cancer case–control (Boice et al, 1988)	338	163 [e]	2	n.a.	0.69 (0.01, 2.25) [f]	3.16 (0.05, 10.4) [g]
3.2.4	Swedish benign breast disease (Mattsson et al, 1997)	14	15.6	0.66	26,493	1.3 (0, 4.4) [h]	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	618	n.a.	0.025	2,388,848	0.305 (−0.44, 1.37)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	899	n.a.	0.19	n.a.	0.20 (0.04, 0.39)	2.1 (0.43, 4.0)
	Females	786	n.a.	0.18	n.a.	0.65 (0.40, 0.95)	3.3 (2.1, 4.7)
3.2.1	Benign gynaecological disease – USA (Inskip et al, 1990) [i]	23	21.8	0.2	71,958	0.27 (−4.25, 4.80) [j]	n.a.

TABLE 3.3 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [k]	33	26.8 [l]	0.23	47,144	1.01 (<–0.2, 2.8)	5.72 (<–2.4, 16)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [m]	127	128 [l]	3.21	287,095	–0.004 (–0.05, 0.05) [h,n]	n.a.
3.3.2	Peptic ulcer (Carr et al, 2002)	47	14.7 [l]	14.8	41,779	0.20 [o] (0, 0.73) [h]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	347	n.a.	0.0194	5,192,710	0.49 (<0, 3.92)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	518	n.a.	0.025	2,433,573	0.336 (–0.51, 1.58)	n.a.
7.1	Yangjiang background radiation (Sun et al, 2000; Tao et al, 2000)	70	76.9	0.0064 [p]	1,231,708	–0.27 (–1.37, 2.69) [h,q]	n.a.
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
8.2	Swedish hyperthyroid patients (Holm et al, 1991)	58 [r]	43.6	0.25	n.a.	1.32	9.6
Mortality							
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	150 [s]	n.a.	0.634 [t]	284,260	0.95 (0.17, 3.49) [h,u]	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
11.1	Radium-224 TB and ankylosing spondylitis patients (Nekolla et al, 1999)	13	~11	n.a.	n.a.	~1.2 (95% CI n.a.)
11.2	Radium-224 ankylosing spondylitis patients (Wick et al, 1999)	18	12.2	n.a.	32,800	1.56 [v] (95% CI n.a.)

TABLE 3.3 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	13	4.8	n.a.	25,475	2.7 (1.1, 7.9) [w]
14.2.1	Drilled well users (Auvinen et al, 2005)	88	n.a.	*Median activity concentration* Radon: 130 Bq l^{-1} Radium: 0.01 Bq l^{-1} Uranium: 0.07 Bq l^{-1}		*RR per log (100 Bq l^{-1})* Radon: 0.68 (0.29, 1.59) Radium: 0.69 (0.33, 1.47) Uranium: 0.92 (0.48, 1.21)
Mortality						
12.1	German Thorotrast patients (van Kaick et al, 1989, 1999; Becker 2008)	25 male 5 female	n.a.	20.6 ml [x]	n.a.	Male: 0.9 (0.5, 1.6) Female: 0.9 (0.3, 2.5) [v]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	54	60.7 [l]	n.a.	n.a.	0.85 (0.60, 1.21) [y]

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e Calculated as the ratio of the observed cases to the estimated relative risk.
f Estimated based on 10-year survivors.
g Calculated using incidence rates estimated for non-exposed women in the related cohort study of Boice et al (1985).
h 95% CI here.
i The observed and expected numbers of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on a Poisson regression model.
j Wald-type confidence interval.
k The values given exclude the period within 5 years of irradiation.
l Based on national mortality rates.
m The values given exclude the period within 5 years of first treatment.
n Dose–response analysis based on the number of treatment courses given.
o Based on a dose–response analysis for patients with more than 10 years of follow-up and with stomach doses less than or equal to 10 Gy.
p Mean annual effective dose.
q Based on a 10-year latent period.
r Restricted to the period 10 or more years after treatment.
s Number of cancers in both the exposed and the comparison group.
t Average cumulative dose in the exposed group, arising from internal and external exposures.
u Based on a dose–response analysis conducted solely within the exposed group.
v Relative to an unexposed comparison group.
w Relative to an unexposed comparison group. Amongst exposed patients, there was no evidence of trend in risk with a measure of cumulative exposure.
x Amount of Thorotrast administered.
y Relative to workers not monitored for any radionuclide.

questionable. The Chinese study of medical X-ray workers showed no excess among those employed before 1970 when exposures were high (estimated mean cumulative dose of 0.55 Gy), but an excess was reported among those first employed during 1970–1980 (estimated mean cumulative dose of 0.08 Gy) (Wang et al, 2002). Among US radiological technologists, both males and females had lower stomach cancer mortality rates (Mohan et al, 2002) and incidence (Sigurdson et al, 2003) than the general population. Rogel et al (2005) reported a deficit (at borderline levels of statistical significance) of stomach cancer mortality compared with French national rates among radiation workers of Électricité de France (3 observed versus 7.2 expected deaths; SMR = 0.41; 90% CI 0.11, 1.07).

The Swedish study of patients treated with iodine-131 for hyperthyroidism reported increased incidence (Holm et al, 1991) and mortality rates (Hall et al, 1992) from stomach cancer, with some indication of a dose–response trend. In general, however, the epidemiological data were too sparse to quantify a dose or dose rate effectiveness factor or to characterise risks from internal low or high LET exposures. A study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan (Bauer et al, 2005) reported a highly statistically significant trend of increasing risk with dose in females ($p = 0.0016$), although not for males ($p = 0.36$). The aggregate ERR based on an internal analysis was 1.68 Sv^{-1} (95% CI 0.83, 2.99); however, when the analysis was restricted to the exposed group, based on individual dose estimates, the ERR estimate was somewhat lower at 0.95 Sv^{-1} (95% CI 0.17, 3.49). As noted previously, ecological bias may operate in this study, so these findings should be treated with caution.

There is a moderate amount of information in relation to internal high LET exposure. Studies of persons exposed to radium-224 (Nekolla et al, 1999; Wick et al, 1999) and Thorotrast (van Kaick et al, 1989, 1999; Andersson et al, 1995) provide little evidence of elevated risks of stomach cancer. A study of 11 cohorts of underground miners found excess mortality rates from stomach cancer in comparison to national and local rates, but no evidence of an increase in mortality rates with increasing cumulative radon exposure (Darby et al, 1995). Because doses to the stomach from radon are estimated to be very low, it seems likely that the excess is due to other factors such as other exposures in mining environments or smoking. Travis et al (2003b) studied patients injected with Thorotrast during radiographic procedures in Denmark, Sweden and the USA. Stomach cancer incidence in a group of Thorotrast-exposed patients in Denmark and Sweden was significantly elevated compared to a control group, but there was no evidence of a trend of increasing stomach cancer incidence with a surrogate measure of cumulative radiation dose. Among US Thorotrast patients, stomach cancer was not evaluated with respect to the mortality rate data that were available for the USA (Travis et al, 2003b).

Auvinen et al (2005) studied stomach cancer in relation to radon, uranium and other radionuclides in drinking water in a cohort of persons who used water from wells drilled into bedrock in Finland. Activity concentrations of radium-226, radon and uranium were assessed from samples from each well by radiometric analysis. There was no relationship seen between stomach cancer incidence and levels of any of the three radionuclides. If anything there was an inverse relationship: the hazard ratio in the group exposed to 130–299 Bq l^{-1} radon relative to the group exposed to less than 130 Bq l^{-1} was 0.54 (95% CI 0.25, 1.18), and the hazard ratio in the group exposed to 300–15,000 Bq l^{-1} radon relative to that exposed to less than 130 Bq l^{-1} was 0.48 (95% CI 0.25, 0.94). Similar inverse relationships between exposure and stomach cancer risk were observed for radium-226 and uranium.

3.4.2.2 Estimates of radiation risks

As given in Table 3.3, the ERR of stomach cancer in the latest Life Span Study incidence data (Preston et al, 2007) for exposure at age 30 is 0.34 Sv^{-1} (90% CI 0.22, 0.47); the corresponding EAR is 9.5 10^{-4} PY^{-1} Sv^{-1} (90% CI 6.1, 14). In the latest mortality data (Preston et al, 2003) the ERR for males is 0.20 Sv^{-1} (90% CI 0.04, 0.39) and for females is 0.65 Sv^{-1} (90% CI 0.40, 0.95); the corresponding EAR for males is 2.1 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.43, 4.0) and for females is 3.3 10^{-4} PY^{-1} Sv^{-1} (90% CI 2.1, 4.7). There are estimates of radiation risk from internal low LET exposure, for cancer incidence in the Swedish study of patients treated with iodine-131 for hyperthyroidism of 1.32 Sv^{-1} (90% CI 0.04, 2.84) (Holm et al,. 1991), and for cancer mortality from the Semipalatinsk study of Bauer et al (2005) an ERR of 0.95 Sv^{-1} (95% CI 0.17, 3.49). Risks in other exposed groups are given in Table 3.3.

3.4.2.3 Modifying factors

There is a statistically significant reduction in stomach cancer relative risk by attained age in the latest Life Span Study incidence data, but no significant variation with age at exposure (Preston et al, 2007). Excess absolute risk increases with attained age in the same dataset.

3.4.2.4 Gaps in knowledge

There is limited information on risks from internal high and low LET radiation exposure. There are only two studies of internal low radiation exposure which yield quantitative risk estimates, and none in relation to internal high LET exposure.

3.5 Colon

3.5.1 General epidemiology

Approximately 22,000 cases and 10,000 deaths from colon cancer occur annually in the UK (Cancer Research UK, 2008). The disease is slightly more common in males than females (age-standardised incidence rate of 21 versus 16 per 100,000 persons for males and females, respectively, in the UK, for 2002). Age-standardised incidence rates are highest in Western countries, especially among the black population in the USA (around 36 per 100,000 in 2002) and lowest in India (around 2 per 100,000) (www-dep.iarc.fr/). Incidence rates have risen slightly in males since 1971 (from 24 per 100,000 to over 30 per 100,000) but there is little trend in females. In contrast, mortality has been declining steadily in both sexes (Quinn and Babb, 2000).

The geographical variation and migrant studies suggest that dietary factors are important determinants of colon cancer risk. There is reasonable evidence that high consumption of red meat is a risk factor, while consumption of fibre is protective (Sandhu et al, 2001; Norat et al, 2002; Park et al, 2005).

3.5.2 Findings from studies of radiation exposure

3.5.2.1 Informative studies and evidence for association and causality

Table 3.4 summarises findings from cohort and case–control studies of colon cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. For external exposure, the strongest evidence is provided by the Life Span Study (Preston et al, 2007). There is a clear excess risk in this study based on both incidence and mortality, and a clear trend in risk by estimated dose.

In medically exposed populations, a significant association, and a significant dose response, was reported in the ankylosing spondylitis study (Weiss et al, 1994) and the cohort of metropathia haemorrhagica patients of Darby et al (1994), and weaker evidence of an association in the study of patients treated for benign gynaecological disease (Inskip et al, 1990) and the metropathia study of Ryberg et al (1990). There was, however, no evidence of an effect in the cervical cancer case–control study of Boice et al (1998) or the study of peptic ulcer patients (Carr et al, 2002) or patients treated for skin haemangiomas (Lundell and Holm, 1995).

None of the major studies of radiation workers showed an excess risk of colon cancer. These include the 15-country (Cardis et al, 2007), UK NRRW (Muirhead et al, 1999, 2009) and Canadian National Dose Registry (Ashmore et al, 1998) studies (see Table 3.4). Similarly, no excess risk was seen among radiation workers of Électricité de France (SMR = 0.97 based on 8 deaths; Rogel et al, 2005).

With regard to medical workers exposed to radiation, neither the study of US radiological technologists (Sigurdson et al, 2003) nor the study of medical X-ray workers in China (Wang et al, 2002) showed an association with colon cancer risk.

There are some data on the effects of high LET radiation exposure on colon cancer risk. Studies of persons exposed to radium-224 (Nekolla et al, 1999; Wick et al, 1999) and Thorotrast (van Kaick et al, 1989, 1999; Andersson et al, 1995; Travis et al, 2003b) showed no evidence of an excess risk, and no effect was seen in the study of UK radiation workers monitored for plutonium (Carpenter et al, 1998). With regard to internal low LET radiation, the Swedish study of patients treated with iodine-131 for hyperthyroidism found no excess risk of colorectal cancer (Holm et al, 1991; Hall et al, 1992). An apparent excess of colon cancer was seen in the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan (Bauer et al, 2005), although this is difficult to evaluate since an explicit analysis for colon cancer was not presented.

3.5.2.2 Estimates of radiation risks

The ERR of colon cancer in the latest Life Span Study incidence data (Preston et al, 2007) is 0.54 Sv^{-1} (90% CI 0.30, 0.81); the corresponding EAR is 8 10^{-4} PY^{-1} Sv^{-1} (90% CI 4.4, 12). The latest Life Span Study mortality data gave a similar ERR estimate of 0.54 Sv^{-1} (90% CI 0.13, 1.2) in males and 0.49 Sv^{-1} (90% CI 0.11, 1.1) in females. The lack of an association following higher medical exposures may reflect cell killing effects at high doses. No good estimates are available for internal exposure.

3.5.2.3 Modifying factors

In the Life Span Study, the relative risk appears to be unrelated to age at exposure. There is some evidence of a decline in ERR (but increase in EAR) with increasing attained age (Preston et al, 2007). The estimated ERR is higher for males (0.73 Sv^{-1}) than for females (0.34 Sv^{-1}), but this difference is not statistically significant and was not seen in the mortality analysis (Preston et al, 2003).

3.5.2.4 Gaps in knowledge

There remains little information on risks related to high LET radiation. While the results from the Life Span Study show a clear risk and a dose–response, the inconsistencies in the results from studies of medical exposures remain unresolved.

TABLE 3.4 Risk estimates for colon cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted colon dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	323	n.a. [a]	0.22	436,180	0.73 (0.38, 1.17) [b]	13.0 (4.4, 16) [b]
	Females	348	n.a.	0.21	729,608	0.34 (0.13, 0.63) [b]	3.0 (6.4, 14) [b]
	Both sexes						
	Age at exposure <20 y	229	n.a.	0.22	586,255	0.52 (0.21, 1.2) [c]	41 (17, 91) [c]
	20–39 y	301	n.a.	0.21	378,204	0.54 (0.30, 0.81) [b]	8.0 (4.4, 12) [b]
	40+ y	141	n.a.	0.20	201,330	0.55 (0.15, 1.2) [d]	1.6 (0.3, 3.9) [d]
	All	671	n.a.	0.21	1,165,788	0.54 (0.30, 0.81) [b]	8.0 (4.4, 12) [b]
2.2.3	Cervical cancer case–control (Boice et al, 1988)	375	368 [e]	24	n.a.	0.00 (−0.01, 0.02) [f]	0.01 (−0.09, 0.18) [g]

TABLE 3.4 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	12	~11 [h]	0.07	406,565	0.37 [i]	0.11
6.4	Canadian National Dose Registry (Sont et al, 2001)	315	349.4	0.0066	2,667,903	2.6 (<0, 7.5)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	899 [j]	n.a.	0.025	2,388,848	−0.026 (−0.52, 0.81)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	122	n.a.	0.19	n.a.	0.54 (0.13, 1.2)	1.1 (0.64, 1.9)
	Females	150	n.a.	0.18	n.a.	0.49 (0.11, 1.1)	0.68 (0.76, 1.3)
3.2.1	Benign gynaecological disease – USA (Inskip et al, 1990) [k]	75	46.6	1.3	71,958	0.51 (−0.08, 5.61)	n.a.
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [l]	47	33 [m]	3.2	47,144	0.13 (0.01, 0.26) [n]	n.a.
3.2.5	Metropathia haemorrhagica – Sweden (Ryberg et al, 1990)	12	8.2 [o]	n.a.	n.a.	1.46 (0.76, 2.56) [n]	n.a.
3.3.2	Peptic ulcer (Carr et al, 2002)	36	26.9 [m]	10	41,779	−0.005 (−0.046,0.067) [n,p]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	410	n.a.	0.0194	5,192,710	0.21 (<0, 3.07)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	588 [j]	n.a.	0.025	2,433,573	−0.126 (−0.75, 0.77)	n.a.

TABLE 3.4 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	16	10.7	n.a.	25,480	1.5 (0.7, 3.0) [q]
Mortality						
12.1	German Thorotrast patients (van Kaick et al, 1989, 1999; Becker et al, 2008)	4 males 2 females	n.a.	20.6 ml [r]	n.a.	Male: 0.3 (0.1, 1.0) Female: 0.6 (0.1, 4.4) [l]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	38	40.4 m	n.a.	n.a.	0.84 (0.55, 1.26) [s]

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years .
d Value applies at attained age 70 years following exposure at age 50 years.
e Calculated as the ratio of the observed cases to the estimated relative risk.
f Estimated based on 10-year survivors.
g Calculated using incidence rates estimated for non-exposed women in the related cohort study of Boice et al (1985).
h Based on cancer incidence rates for Stockholm.
i Not statistically significantly different from zero.
j Cancer of the large intestine: ICD9 153 and 159.0.
k The observed and expected numbers of cases are for 10-year survivors. The estimated number of expected cases incorporated an adjustment based on a Poisson regression model.
l The values given exclude the period within 5 years of irradiation.
m Based on national mortality rates.
n 95% CI here.
o Based on incidence data from the Swedish National Cancer Registry
p Based on patients with more than 10 years of follow-up and dividing the overall ERR by the average dose.
q Relative to an unexposed comparison group.
r Amount of Thorotrast administered.
s Relative to workers not monitored for any radionuclide.

3.6 Rectum

3.6.1 General epidemiology

Approximately 14,000 cases and 6,000 deaths from rectal cancer occur annually in the UK (Cancer Research UK, 2008). The disease is more common in males than in females (age-standardised incidence rates 15 versus 8 per 100,000 in the UK, 2002). Age-standardised incidence rates are highest in Western countries and Japan (over 20 per 100,000 in males and around 10 per 100,000 in females) and lowest in India (around 2 per 100,000) (www-dep.iarc.fr/). Incidence rates in the UK have been fairly stable since 1971, but mortality has fallen (Quinn and Babb, 2000).

As for colon cancer, geographical variation is presumed to reflect differences in diet. However, many studies do not separate colon and rectal cancer and specific evidence on risk factors is less clear for rectal cancer.

3.6.2 Findings from studies of radiation exposure

3.6.2.1 Informative studies and evidence for association and causality

Table 3.5 summarises findings from cohort and case–control studies of colon cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. In the most recent analysis of the Life Span Study, the risk for rectal cancer was not significantly increased over background rates, and there was no evidence of a dose response (Preston et al, 2007). In the corresponding mortality analysis, rectal cancer mortality was lower than expected (Preston et al, 2003).

Among studies of medically exposed individuals, no association was found in females treated with radiation for cervical cancer (Boice et al, 1998), or in the cohorts of ankylosing spondylitis (Weiss et al, 1994), metropathia haemorrhagica (Ryberg et al, 1990; Darby et al, 1994) or patients treated for benign gynaecological disease (Inskip et al, 1990). However, an increased risk of rectal cancer has been observed in males irradiated for prostate cancer (Baxter et al, 2005).

In studies of radiation workers, the 15-country (Cardis et al, 2007) and Canadian National Dose Registry (Ashmore et al, 1998) studies show no excess risk of rectal cancer mortality. However, the most recent analysis of the UK NRRW study (Muirhead et al, 2009) found evidence of excess mortality and incidence. The study by Iwasaki et al (2003) found no overall risk of rectal cancer, but did find some evidence of an increasing SMR with increasing dose ($p = 0.02$). With regard to medical workers, the study of US radiological technologists showed a marked decreased risk of rectal cancer (Sigurdson et al, 2003), while Wang et al (2002) found no effect in their study of medical X-ray workers in China.

There are few data on the effects of internal exposure on rectal cancer risk. Studies of persons exposed to radium-224 (Nekolla et al, 1999; Wick et al, 1999) and Thorotrast (van Kaick et al, 1989, 1999; Andersson et al, 1995; Travis et al, 2003b) showed no evidence of an excess risk, and no effect was seen in the study of UK radiation workers monitored for plutonium (Carpenter et al, 1998). With regard to internal low LET radiation, the Swedish study of patients treated with iodine-131 for hyperthyroidism found no excess risk of colorectal cancer (Holm et al, 1991; Hall et al, 1992). No excess was seen in the study of persons exposed to weapons test fallout in the Semipalatinsk area of Kazakhstan (Bauer et al, 2005).

TABLE 3.5 Risk estimates for rectal cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted bladder dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	376	n.a. [a]	0.21	1,165,788	0.19 (−0.04, 0.47)	0.56 (−0.13, 1.4)
2.2.3	Cervical cancer case–control (Boice et al, 1988)	465	254 [b]	30–60	n.a.	0.02 (0.00, 0.04) [c]	0.06 (0.00, 0.16) [d]
6.4	Canadian National Dose Registry (Sont et al, 2001)	145	199.0	0.0066	2,667,903	13.8 (3.7, 33.6)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	586	n.a.	0.025	2,388,848	1.307 (0.21, 2.85)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	96	n.a.	0.19	n.a.	−0.25 (<−0.3, 0.15)	−0.41 (<−0.4, 0.22)
	Females	127	n.a.	0.18	n.a.	0.75 (0.16, 1.6)	0.69 (0.16, 1.3)
3.2.1	Benign gynaecological disease – USA (Inskip et al, 1990) [e]	15	15.2	3.0	71,958	0.03 (−0.14, 0.19)	n.a.
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [f]	14	12.4 [g]	4.9	47,144	0.04 (−0.09, 0.16) [h]	n.a.
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [i]	62	56.9 [g]	4.12	287,095	0.03 (−0.03, 0.10) [h,j]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	185	n.a.	0.0194	5,192,710	1.27 (<0, 7.62)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	303	n.a.	0.025	2,433,573	1.69 (0.19, 4.12)	n.a.

TABLE 3.5 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	8	8	n.a.	25,480	1.8 (0.6, 5.3) [k]
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	6 males 6 females	n.a.	20.6 ml [l]	n.a.	Males: 1.1 (0.3, 3.5) Females: 1.1 (0.1, 15.3)
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	25	28.7 [g]	n.a.	n.a.	1.02 (0.59, 1.75) [m]

Notes
a Not available.
b Calculated as the ratio of the observed cases to the estimated relative risk.
c Estimated based on 10-year survivors.
d Calculated using incidence rates estimated for non-exposed women in the related cohort study of Boice et al (1985).
e The observed and expected numbers of cases are for 10-year survivors.
f The values given exclude the period within 5 years of irradiation.
g Based on national mortality rates.
h 95% CI here.
i The values given exclude the period within 5 years of first treatment.
j Dose–response analysis based on the number of treatment courses given.
k Relative to an unexposed comparison group.
l Amount of Thorotrast administered.
m Relative to workers not monitored for any radionuclide.

3.6.2.2 Estimates of radiation risks

Based on the latest Life Span Study data, the ERR of rectal cancer is 0.19 (90% CI −0.04, 0.47), the corresponding EAR being 0.56 10^{-4} PY^{-1} Sv^{-1} (90% CI −0.13, 1.4).

3.6.2.3 Modifying factors

Based on the Life Span Study data, there is no evidence of a trend in risk by age at exposure or attained age, and no evidence for a higher risk in males or females.

3.6.2.4 Gaps in knowledge

Given the clear association between radiation and colon cancer risk, it is plausible that the association seen in the Life Span Study, though not significant, is real. The magnitude of the association is unclear and, if any, is weaker than for colon cancer. There is little evidence on risks associated with internal high or low LET radiation.

3.7 Liver

3.7.1 General epidemiology

Liver cancer is the third most common cause of cancer death worldwide, but is relatively rare in the UK (Parkin et al, 2005). Liver cancer is highly fatal, but the mortality data are unreliable because metastatic cancers from other organs are often misclassified as liver cancer at death certification. Only a little over 50% of liver cancers reported on death certificates in the USA are attributable to primary liver cancer (Percy et al, 1990). Misclassified diagnoses can either underestimate or overestimate the association with radiation exposure, depending upon the organs from which cancer metastases occurred. The two major types of primary liver cancer are liver cell (or hepatocellular) carcinoma (HCC) and cholangiocarcinoma, which differ in aetiology and pathology. In the UK, there have been reported 30–50% increases in overall liver cancer mortality and incidence rates, with a more marked increase in cholangiocarcinoma, in the last two decades (West et al, 2006).

Liver cell carcinomas are the predominant type of liver cancer in many populations and attributable largely (80–95%) to infection with hepatitis B or C virus (Parkin, 2006). Worldwide, hepatitis B virus infection is more prevalent than hepatitis C viral infection, except for Japan where liver cancers are mostly attributable to hepatitis C viral infection (Tanaka et al, 1994; Parkin et al, 2005). Excessive alcohol consumption is an acknowledged cause of HCC (IARC, 1988), but how alcohol consumption interacts with hepatitis viral infection in the pathogenesis of liver cell carcinoma is not well understood. Aflatoxin, a product of the fungus *Aspergillus* species, is an important cause of liver cancer in geographical areas where contamination of food with this toxin is common. Cholangiocarcinomas originating from the intrahepatic bile duct are likely to be similar to cancer of the extrahepatic bile duct and gallbladder cancer in their aetiology, and are more frequent in females than in males. High rates of cholangiocarcinoma have been linked to the endemic occurrence of liver fluke infection in certain areas of Thailand (Parkin et al, 2005; Thomas et al, 2006).

3.7.2 Findings from studies of radiation exposure

3.7.2.1 Informative studies and evidence for association and causality

Table 3.6 summarises findings from cohort studies of radiation-exposed populations for which individual dose estimates are available. Because of the concern for disease misclassification with liver cancer mortality data, the most informative studies are those in which the occurrence of liver cancers is ascertained with medical validation and with histological and other diagnostic confirmation. For low LET radiation exposures, the most informative are the Life Span Study of the Japanese atomic bomb survivors (Thompson et al, 1994; Preston et al, 2007) and studies of two medically exposed populations, ie patients irradiated for cervical cancer or benign breast disease (Boice et al, 1985; Mattsson et al, 1997) for which the follow-up was based on cancer incidence data. The Life Span Study incidence data are particularly informative because the effects of radiation were assessed for primary liver cancer based on pathology reviews (Cologne et al, 1999). While studies of medically and occupationally exposed populations have not demonstrated an association between liver cancer and exposure to low LET radiation, the Life Span

TABLE 3.6 Risk estimates for liver cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted liver dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	394	n.a.[a]	0.22	436,180	0.32 (0.12, 0.60)[b]	6.4 (0.2, 12)[b]
	Females	252	n.a.	0.21	729,608	0.28 (0.05, 0.63)[b]	2.1 (0.6, 4.3)[b]
	Both sexes						
	Age at exposure <20 y	260	n.a.	0.22	586,255	0.28 (0.06, 0.78)[c]	6.8 (0.0, 22)[c]
	20–39 y	221	n.a.	0.21	378,204	0.30 (0.11, 0.55)[b]	4.3 (0.0, 7.2)[b]
	40+ y	165	n.a.	0.20	201,330	0.32 (0.07, 0.85)[d]	2.6 (0.5, 6.4)[d]
	All	646	n.a.	0.21	1,165,788	0.30 (0.11, 0.55)[b]	4.3 (0.2, 7.2)[b]
2.2.1	Cervical cancer cohort (Boice et al, 1985)	8	8.8	1.50	178,243	−0.06 (−0.37, 0.4)	−0.03 (−0.16, 0.2)
3.2.4	Swedish benign breast disease (Mattsson et al, 1997)	12	11.3	0.66	26,493	0.09 (<0, 1.4)[e]	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	86	n.a.	0.025	2,388,848	−0.32 (< −1.93, 6.58)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	408	n.a.	0.20	n.a.	0.39 (0.11, 0.68)	2.4 (1.2, 4.0)
	Females	291	n.a.	0.19	n.a.	0.35 (0.07, 0.72)	0.85 (0.18, 1.6)
3.3.2	Peptic ulcer (Carr et al, 2002)	11	6.1[f]	4.8	41,779	−0.16 (0.69, 1.48)[e,g]	n.a.

TABLE 3.6 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	62	n.a.	0.0194	5,192,710	6.47 (<0, 27.0)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	89	n.a.	0.025	2,433,573	1.87 (−1.19, 8.28)	n.a.
7.1	Yangjiang background radiation (Sun et al, 2000; Tao et al, 2000)	171	214	0.0064 [h]	1,231,708	−0.99 (−1.60, 0.10) [e,i]	n.a.
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Mortality							
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	60 [j]	n.a.	0.634 [k]	284,260	−0.08 (−0.41, 1.00) [e,l]	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	136 [m]	1.2 [n]	n.a.	25,480	Infinity (44.2, infinity) [o]
Mortality						
12.1	German Thorotrast patients (van Kaick et al, 1995, 1999; Becker et al, 2008)	238 male 41 female	3.6	4.9	n.a.	Males: 71 (32, 195) Females: 34 (8.9, 292) [p]
12.2	International Thorotrast cohort – US patients (Travis et al, 2003b)	22	1.2 [f]	n.a.	8,740	22.5 (1.8, 464.3)
12.3	Portuguese Thorotrast patients (dos Santos Silva et al, 2003) [q]	67	0.2 [f,i]	20 ml [r] (median)	13,283	42.4 (13.90, 210) [s]

TABLE 3.6 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
A12.1, A12.2	Combined Japanese Thorotrast patients (Mori et al, 1999)	143	4	n.a.	10 685	n.a.
13.2.1	Mayak plutonium workers (Gilbert et al, 2000; Sokolnikov et al, 2008)	40 [t]	n.a.	n.a.	84,593	Males: 2.6 (0.7, 6.9) Females: 29 (9.8, 95) [u]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	6 [g]	8.6 [f]	n.a.	n.a.	2.00 (0.59, 6.38) [v]

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e 95% CI here.
f Based on national mortality rates.
g Based on patients with more than 10 years of follow-up.
h Mean annual effective dose.
i Based on a 10-year latent period.
j Number of cancers in both the exposed and the comparison group.
k Average cumulative dose in the exposed group, arising from internal and external exposures.
l Based on a dose–response analysis conducted solely within the exposed group.
m Cases of primary liver cancer.
n Based on national incidence rates.
o Relative to an unexposed comparison group. Amongst exposed patients, there was strong evidence of an increasing trend in risk with a measure of cumulative exposure ($p<0.001$).
p Relative to comparison group.
q Based on follow-up and deaths 5 years or more following the first examination.
r Amount of Thorotrast administered.
s Relative to a group of unexposed patients, among whom 3 deaths occurred compared with 0.38 expected.
t Among workers with plutonium body burdens of more than 7.4 kBq.
u Excess relative risk per Gy.
v Relative to workers not monitored for any radionuclide.

Study incidence data provide evidence of a dose response for liver cancer, primarily for liver cell carcinoma (Cologne et al, 1999). This association found in the Life Span Study is unlikely to be confounded by hepatitis B or C viral infection because the viral infection rates are not associated with radiation doses (Fujiwara et al, 2000, 2003).

Follow-up studies of patients administered Thorotrast for diagnostic purposes in Germany, Portugal, Denmark, Sweden, Japan and the USA are all informative in assessing cancer risks associated with internal exposure to high LET alpha radiation. Some of these studies are based on mortality follow-up alone or supplemented by medical follow-up, but studies in Sweden (Nyberg et al, 2002) and Denmark (Andersson et al, 1992) evaluated cancer incidence data and have been incorporated in a combined analysis together

with US mortality data (Travis et al, 2003b). A significant dose–response relationship has been demonstrated by several cohorts for the incidence of liver cancer and a measure of cumulative radiation dose. Radiation doses from Thorotrast are non-uniformly distributed, with the liver and the bile ducts receiving especially high doses from alpha radiation. This is consistent with the uniquely high proportion of cholangiocarcinomas and haemangiosarcomas in the liver cancers in the exposed patients (Sharp, 2002). From these studies, a causal association between Thorotrast and cholangiocarcinoma and haemangiosarcoma can be concluded.

There is evidence of increased liver cancer associated with exposure to internally deposited plutonium from studies of the workers at the Mayak production facility in Russia (Gilbert et al, 2000). The risk of liver cancer incidence increasing with estimated plutonium body burden after adjustment for external gamma radiation, together with the large relative risk associated with high plutonium burdens in the Mayak cohort, strongly suggest that this association is causal and is unlikely due to confounding by alcohol consumption. The lack of supporting data from previous studies of plutonium workers in the USA and UK (Wilkinson et al, 1987; Gilbert et al, 1989; Voelz et al, 1991; Omar et al, 1998, 1999; Wiggs et al, 1999) is probably due to the much lower levels of plutonium exposure in US and UK workers compared to the Mayak workers.

Based on the dose response and other data from the Life Span Study cohort, a causal association can be concluded between low LET radiation exposures and liver cell carcinoma. Based on studies of several cohorts exposed to Thorotrast and plutonium, it can also be concluded that internal high LET radiation exposure is causally associated with liver cancer, especially cholangiocarcinoma and haemangiosarcoma.

3.7.2.2 Estimates of radiation risks

The Life Span Study tumour-registry based incidence data show a significant linear dose response with no indication of non-linearity for liver cancer (Thompson et al, 1994; Preston et al, 2007). The ERR at 1 Gy is estimated to be 0.30 and does not differ significantly between males and females (Preston et al, 2007). Excess liver cancers in the Life Span Study mostly involve hepatocellular carcinomas, which are the majority (85%) of primary liver cancers (Cologne et al, 1999; Fukuhara et al, 2001).

In many of the Thorotrast studies, the relative risk of liver cancer was found to increase with increasing amounts of injected Thorotrast, which was used as a surrogate measure of cumulative radiation dose. Quantitative estimation of the risk associated with radiation dose is complicated by the uneven distribution of doses within the organ/tissue and the possibility that, in long-term irradiation from internally deposited radionuclides, initiated tumours may be dormant over an extended period of time so that the doses received several years before diagnosis of clinical cancer may be irrelevant for cancer induction ('wasted dose (time)'). Assuming a wasted dose of 10 years, van Kaick et al (1999) estimated the cumulative risk of 607 per 10^4 person-years per gray in the German Thrororotrast cohort. Similar estimates were reported from studies of the Danish cohort (510 per 10^4 person-years per gray) (Andersson et al, 1997) and the Japanese cohort (523 per 10^4 person-years per gray) (Mori et al, 1999).

In the Mayak cohort, the relative risk of liver cancer increased significantly with increasing plutonium body burden and was significantly elevated (relative risk of 17) among those with body burdens exceeding 7.4 kBq (mean; 20 kBq for males and 46 kBq for females). Further quantification of the liver cancer risk was considered unwarranted at this time because of the limitations in the plutonium dosimetry (Gilbert et al, 2000).

3.7.2.3 Modifying factors

The case–control data suggest an interactive (multiplicative) effect of hepatitis C viral infection on the liver cell carcinoma risk associated with radiation exposure (Sharp et al, 2003). The Life Span Study data provide no evidence of interaction between hepatitis B viral infection and hepatocellular carcinoma risk, but this may be due to the low prevalence of this infection in this cohort. These case–control findings based on autopsied subjects need to be interpreted with caution, but may offer an explanation for the absence of a demonstrable risk for liver cancer in other irradiated populations where hepatitis viral infection is insignificant. The Life Span Study cohort data (Preston et al, 2007) show little or no evidence of the excess relative risk in individuals exposed before 10 years of age. The risk is significantly increased among those exposed after age 10, but in this age group the ERR does not vary with age at exposure. The ERR is similar in males and females. However, the EAR is about three times higher in males than females as the baseline rates for males are also three or four times higher than for those for females.

3.7.2.4 Gaps in knowledge

Analyses of the interaction between low LET radiation exposure and hepatitis viral infection for the risk of liver cell carcinoma should be repeated with updated incident cases in the Life Span Study and reproduced in other populations. Possible modifying effects of other risk factors, especially alcohol consumption, need to be investigated.

The plutonium dosimetry in the Mayak workers should be refined to improve risk estimation for internal exposure to high LET radiation.

3.8 Pancreas

3.8.1 General epidemiology

Pancreatic cancer is relatively rare in the UK; however, because of its very high fatality rate it is the sixth most common cause of death from cancer (Cancer Research UK, 2008). Time trends and geographical differences in incidence and mortality rates partly reflect variations in smoking, which is one of the only established risk factors. Age-standardised incidence and mortality rates are similar because of the high fatality rate, and in males the annual rates have decreased from 12 per 100,000 population in 1971 to 10 per 100,000 in 2003, whilst the corresponding rates in females have remained stable at about 7 per 100,000 population. Most pancreatic cancers are adenocarcinomas originating from the exocrine part of the pancreas.

The causes of pancreatic cancer in the general population are not well understood. Aside from cigarette smoking, which is a relatively weak risk factor for pancreatic cancer (relative risk for current smoking of about 2), there is some epidemiological evidence that a prior history of diabetes is also a cause and not just a consequence of pancreatic cancer (Huxley et al, 2005).

TABLE 3.7 Risk estimates for pancreatic cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted pancreas dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	229	n.a. [a]	0.21	1,165,788	0.26 (−0.07, 0.68)	0.46 (−0.13, 1.5)
2.2.3	Cervical cancer case–control (Boice et al, 1988)	211	152 [b]	1.9	n.a.	0.00 (−0.28, 1.62) [c]	0.00 (−0.65, 1.43) [d]
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	9	2.7 [e]	0.09	406,565	25.1 (5.5, 57.7) [f]	1.7
3.2.4	Swedish benign breast disease (Mattsson et al, 1997)	14	11.0	0.37	26,493	−0.37 (<0, 0.8) [f]	n.a.
6.4	Canadian National Dose Registry (Sont et al, 2001)	76	101.1	0.0066	2,667,903	6.9 (<0, 27.1)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	320	n.a.	0.025	2,388,848	0.08 (−0.95, 9.26)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	103	n.a.	0.19	n.a.	−0.11 (<−0.3, 0.44)	−0.15 (<−0.4, 0.58)
	Females	135	n.a.	0.18	n.a.	−0.01 (−0.28, 0.45)	−0.01 (−0.35, 0.52)
3.3.2	Peptic ulcer (Carr et al, 2002)	37	13.4 [g]	13.5	41,779	0.34 (0.09, 0.89) [f,h]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	272	n.a.	0.0194	5,192,710	2.10 (−0.59, 6.77)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	330	n.a.	0.025	2,433,573	−0.049 (−1.0, 1.64)	n.a.

TABLE 3.7 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	11	2.9	n.a.	25,480	3.8 (1.3, 12.3) [i]
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	15 male 3 female	5.2	4.9	n.a.	Males: 5.5 (1.7, 22.7) Females: 1.3 (0.2, 9.6) [j]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	19	27.9 [g]	n.a.	n.a.	0.72 (0.40, 1.27) [k]

Notes

a Not available.
b Calculated as the ratio of the observed cases to the estimated relative risk.
c Estimated based on 10-year survivors.
d Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
e Based on cancer incidence rates for Stockholm.
f 95% CI here.
g Based on national mortality rates.
h Based on a dose–response analysis for patients (14 cases) with more than 10 years of follow-up and with doses to the pancreas less than or equal to 9 Gy.
i Relative to an unexposed comparison group. Amongst exposed patients, there was evidence of an increasing trend in risk with a measure of cumulative exposure ($p = 0.05$).
j Relative to comparison group.
k Relative to workers not monitored for any radionuclide.

3.8.2 Findings from studies of radiation exposure

3.8.2.1 Informative studies and evidence for association and causality

Table 3.7 summarises findings from cohort and case–control studies of pancreatic cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. As well as these studies, information is available from studies that lack individual assessments – for example, the study by Berrington et al (2001) of British radiologists.

Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the most informative studies are the Life Span Study of the Japanese atomic bomb survivors and the study of females with cervical cancer treated with radiotherapy. These and the combined study of nuclear workers are the only studies with more than 100 cases or deaths; most of the remaining studies have low precision.

Based on the epidemiological evidence from the studies listed in Table 3.7 and the other studies mentioned above, it is unclear whether there is an association between radiation exposure and pancreatic cancer. Most of the studies that suggest a possible association have low precision. Several of the larger studies, including the study of cervical cancer patients and the mortality data from the Life Span Study suggest that there may be no association with radiation exposure. Pancreatic cancer is difficult to diagnose accurately and the histological verification of cases in the Life Span Study was amongst the lowest of any cancer site (52%). Misclassification of outcome could be an explanation for the lack of dose response. Two studies of radiotherapy patients in which the pancreas received a very high radiation dose have found significantly elevated risks of pancreatic cancer, although the studies lacked individual dose assessments (Carr et al, 2002; Travis et al, 2005b).

3.8.2.2 Gaps in knowledge

There is relatively little information on the effect of radiation exposure and pancreatic cancer.

3.9 Trachea, Bronchus and Lung

3.9.1 General epidemiology

Lung cancer is one of the most common cancers in the UK and is the most common cause of death from cancer (Cancer Research UK, 2008). Differences in incidence and mortality rates by age, time and geographical area largely reflect variations in cigarette smoking, which is by far the most important risk factor. For example, annual mortality rates at ages 65–74 years in males have decreased from just under 6 per 1000 population in the mid-1970s to just under 3 per 1000 in 2003, whilst the corresponding rates in females have increased from about 0.9 per 1000 population in 1975 to 1.5 per 1000 in 2003, reflecting changes in smoking habits over time (Cancer Research UK, 2008).

Aside from cigarette smoking and ionising radiation, other risk factors include exposure to industrial carcinogens such as asbestos, radon, arsenic, polycyclic hydrocarbons, nickel and chromium (Cancer Research UK, 2008). Heavy occupational exposure to diesel exhaust probably increases risk and outdoor air pollution may also make a small contribution to the disease burden (1–2% of lung cancer cases). Intake of fruit and, to a lesser extent, vegetables may have a slight protective effect. Previous lung disease (eg tuberculosis and pneumonia) has been related to an increased risk but would account for a very small proportion of lung cancer cases (Cancer Research UK, 2008).

3.9.2 Findings from studies of radiation exposure

3.9.2.1 Informative studies and evidence for association and causality

Table 3.8 summarises findings from cohort and case–control studies of lung cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. As well as these studies, information is available from studies that lack individual assessments – for example, the study by Darby et al (2005b), which included about 115,000 females who received radiotherapy for early breast cancer.

Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the most informative studies regarding radiation exposure are the case–control studies of radon in homes. A particular strength of these studies is that there is very detailed information on each individual's smoking history. In contrast, for the Life Span Study of the Japanese atomic bomb survivors and for most of the other studies of external radiation, smoking information is limited.

Based on the epidemiological evidence from the studies listed in Table 3.8 and the other studies mentioned above, it can be concluded that there is clear evidence of an association between radiation exposure and lung cancer. Furthermore, since there is evidence of dose–response relationships in many of these studies, it can be concluded that this association is causal. The findings from the residential radon studies are remarkably consistent. Apparent inconsistencies in estimates of the magnitude of radiation risk in other studies are probably due to an inability to take adequate account of the effect of smoking in the analysis.

3.9.2.2 Estimates of radiation risks

Various studies indicate that lung cancer rates increase with increasing level of radiation dose. In particular, combined analysis of case–control data on radon in homes (Darby et al, 2005a) indicates a linear dose–response relationship with no threshold at low doses.

For external radiation, the best estimate of risk in relation to radiation exposure is that given by Preston et al (2007) based on cancer incidence among the Japanese atomic bomb survivors, namely an ERR of 0.81 (90% CI 0.56, 1.1). For radon, it would be best to take the estimate after including the effect of year-to-year variability, ie an ERR of 16% per 100 Bq m^{-3} (95% CI 5, 31). As outlined by Little et al (2007), it is possible to convert this last figure into an ERR Sv^{-1}. For example, assuming the aggregate measure of 0.16 per 100 Bq m^{-3} and the conversion factor of 0.13 WLM y^{-1} per 100 Bq m^{-3} (Strom et al, 1996) and then assuming a 30-year (5–35 years before exposure) mean occupancy of houses, and using the mean of correction factors (17.2 mSv WLM^{-1} and 22.5 mSv WLM^{-1}) calculated by Birchall and James (1994) yields a figure of 0.16/[(30 x 0.13) x (0.0172 + 0.0225)/2] = 2.07 Sv^{-1}. Table 3.9 shows values derived by several authors to convert radon exposures expressed in Working Level Months (WLM) or in terms of annual exposures to concentrations expressed as becquerels per cubic metre (Bq m^{-3}).

3.9.2.3 Modifying factors

Several analyses have examined how radiation risks might be modified by other factors, such as age, sex and exposures to agents other than radiation. In particular, the residential radon studies suggest no effect of age, sex or smoking on the ERR per 100 Bq m^{-3}. (It should be noted that this implies much larger absolute risks for smokers than for non-smokers.) Few other studies have high quality smoking information. The AGIR has produced a report on risks lung cancer risk from radon (AGIR, 2009a) that provides further useful discussion.

3.9.2.4 Gaps in knowledge

There is little information on the effect of exposure to radon in childhood. However, there is no evidence at all from the residential studies of an increased ERR per 100 Bq m^{-3} for exposures at younger ages. The apparent increase in the miners' studies may be due to residual confounding with smoking, due to inadequate adjustment for smoking. For external radiation, more information on the combined risk of smoking and lung cancer would be informative (eg as in the analysis of data for the Life Span Study cohort by Pierce et al, 2003).

TABLE 3.8 Risk estimates for lung cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted lung dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	368	n.a. [a]	0.22	436,180	0.28 (0.12, 0.49) [b]	6.0 (2.3, 11) [b]
	Females	337	n.a.	0.21	729,608	1.33 (0.91, 1.8) [b]	9.1 (6.4, 12) [b]
	Both sexes						
	Age at exposure <20 y	140	n.a.	0.22	586,255	0.56 (0.26, 1.1) [c]	7.3 (3.4, 14) [c]
	20–39 y	316	n.a.	0.21	378,204	0.81 (0.56, 1.1) [c]	7.5 (5.1, 10) [c]
	40+ y	249	n.a.	0.20	201,330	1.15 (0.69, 1.8) [d]	7.8 (4.6, 12) [d]
	All	789	n.a.	0.21	1,165,788	0.81 (0.56, 1.1) [b]	7.5 (5.1, 10) [b]
2.2.4	Lung cancer following breast cancer (Inskip et al, 1994)	17	n.a.	15.2 [e]	n.a.	0.20 (−0.62, 1.03) [f,g]	n.a.
2.2.9	Lung cancer following Hodgkin disease (international II) (Gilbert et al, 2003)	146 [h]	n.a.	32 (median)	n.a.	0.15 (0.057, 0.39) [f]	n.a.
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	11	~ 9 [i]	0.12	406,565	1.4 [j]	0.33
3.2.4	Swedish benign breast disease (Mattsson et al, 1997)	10	11.2	0.75	26,493	0.38 (<0, 0.6) [e]	n.a.
6.4	Canadian National Dose Registry (Sont et al, 2001)	476	717.1	0.0066	2,667,903	3.0 (0.5, 6.8)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	2412	n.a.	0.025	2,388,848	0.129 (−0.33, 0.69)	n.a.

TABLE 3.8 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	406	n.a.	0.21	666,870	0.48 (0.23, 0.78)	2.7 (1.4, 4.1)
	Females	348	n.a.	0.20	1,061,690	1.1 (0.68, 1.6)	2.5 (1.6, 3.5)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [k]	563	469 [l]	2.54	287,095	0.05 (0.002, 0.09) [f,m]	n.a.
3.3.2	Peptic ulcer (Carr et al, 2002)	125	62.8 [l]	1.8	41,779	0.24 (−0.08, 0.68) [f,n]	8.27 (5.48, 11.4) [f,o]
4.3	Canadian TB fluoroscopy (Howe, 1995) [p]	455	473.7 [l]	1.02	672,071	0.00 (−0.06, 0.07) [f]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	1,457	n.a.	0.0194	5,192,710	1.86 (0.49, 3.63)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	2337	n.a.	0.025	2,433.573	0.163 (−0.3, 0.72)	n.a.
6.6	Portsmouth naval shipyard: lung cancer study (Yiin et al, 2007)	321 [q] 1,097 [r]	n.a.	0.0226 [s] 0.0242 [t]	n.a.	1.9 (−0.9, 6.6) [f,s,u] 1.6 (−0.6, 4.8) [f,t,u]	n.a.
7.1	Yangjiang background radiation (Sun et al, 2000; Tao et al, 2000)	62	76.5	0.0064 [v]	1,231,708	−0.68 (−1.58, 1.66) [f,w]	n.a.
13.2.1	Mayak plutonium workers (analysis by external dose, adjusted for plutonium exposure) (Gilbert et al, 2004)					*At attained age 60*	*At attained age 60*
	Males	594	n.a.	0.80	485,862	0.17 (0.052, 0.32) [f]	2.4 (0.56, 4.4) [f]
	Females	61	n.a.	0.82	184,616	0.32 (<0,1.3) [f]	0.43 (<0, 1.6) [f]
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Mortality							
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	130 [x]	n.a.	0.634 [y]	284,260	1.76 (0.48, 8.83) [f,z]	n.a.

TABLE 3.8 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean exposure (WLM)	Person-years of follow-up	Excess relative risk at 100 WLM [aa] (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES (occupational radon)						
Mortality						
13.4.1	Chinese tin miners (Xuan et al, 1993; Lubin et al, 1995)	936	n.a.	277.4	135,357	0.16 (0.1, 0.2)
13.4.1	West Bohemia uranium miners (Lubin et al, 1995; Tomasek, 2003)					
	S – cohort	834	183	152	117,273	2.7 [bb]
	N – cohort	81	57	7	144,155	
13.4.1	Colorado Plateau uranium miners (Hornung et al 1987, 1998; Lubin et al 1995)	377	n.a.	822 (median 430)	73,509 [cc]	0.42 (0.3–0.7)
13.4.1	Ontario uranium miners (Kusiak et al, 1991; Lubin et al, 1995)	282	n.a.	30.8	319,701	0.89 (0.5, 1.5)
13.4.1	Newfoundland fluorspar miners (Villeneuve et al, 2007)	191	62 [dd]	378	59,797	0.43 (0.23, 0.62)
13.4.1	Swedish iron miners (Radford et al, 1984; Lubin et al 1995)	79	n.a.	80.6	32,452	0.95 (0.1, 4.1)
13.4.1	New Mexico uranium miners (Samet et al, 1991; Lubin et al, 1995)	68	17 [ee]	110.3	46,797	1.72 (0.6, 6.7)
13.4.1	Beaverlodge uranium miners (Howe et al, 1986; Lubin et al, 1995; Howe and Stager, 1996)	56	n.a.	81.3 [ff]	68,040	3.25 (1.0, 9.6) [gg]
13.4.1	Port Radium uranium miners (Howe et al, 1987; Lubin et al, 1995)	39	n.a.	242.8	31,454	0.19 (0.1, 0.6)
13.4.1	Radium Hill uranium miners (Woodward et al, 1991; Lubin et al, 1995)	32	n.a.	7.6	25,549	5.06 (1.0, 12.2)

TABLE 3.8 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean exposure (WLM)	Person-years of follow-up	Excess relative risk at 100 WLM [aa] (with 95% CI)
A13.4.2	French uranium miners (Laurier et al, 2004)	85	45.1 [l]	71.3	56,372	0.47 (−0.05, 0.98)
A13.4.3	Cornish tin miners (Hodgson and Jones, 1990; Darby et al, 1995)	82	n.a.	65	66,900	0.045 [hh]
13.4.3	German uranium miners (Grosche et al, 2006)	2,201	n.a.	280.2	1,565,070	0.21 (0.18, 0.24)

Study no.	Study	Number of observed cases	Number of expected cases	Mean radon concentration (Bq m^{-3})	Person-years of follow-up	Excess relative risk at 100 Bq m^{-3} [ii] (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES (residential radon)						
Incidence						
14.1.1	European pooling (Darby et al, 2005a, 2006)					
	All persons	7,148	n.a.	97 [jj]	n.a.	0.16 (0.05, 0.31) [kk]
	Current cigarette smokers					0.10 (<0.03, 0.38)
	Ex−smokers					0.22 (0.02, 0.57)
	Lifelong non-smokers					0.20 (0.02, 0.52)
14.1.2	North American pooling (Krewski et al, 2005, 2006)	4,081	n.a.	n.a.	n.a.	0.10 (−0.01, 0.26)
14.1.3	Chinese pooling (Lubin et al, 2004b)	1,050	n.a.	122 and 228 [ll]	n.a.	0.13 (0.00, 0.36)

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES (other than radon)						
Incidence						
11.2	Radium-224 ankylosing spondylitis patients (Wick et al, 1999)	25	35.7	n.a.	32,800 [mm]	1.20 [nn]

TABLE 3.8 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)	
Mortality							
12.1	German Thorotrast patients (van Kaick et al, 1995, 1999; Becker et al, 2005)	42 male 6 female	n.a.	20.6 ml [oo]	n.a.	Males: 1.1 (0.7, 1.7) Females: 1.2 (0.3, 4.5) [pp]	
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	28	13.3	n.a.	25,480	1.3 (0.7, 2.2) [hh]	
A12.1	Japanese Thorotrast patients – combined data (Mori et al, 1999a)	11	n.a.	17 ml [qq]	10,685	2.0 (90% CI 1.0, 3.9)	
12.3	Portuguese Thorotrast patients (dos Santos Silva et al, 2003) [rr]	4	2.1 j	Median 20 ml [aa]	13,283	9.07 (0.90, 447) [ss]	
13.2.1	Mayak plutonium workers (analysis by external dose, adjusted for plutonium exposure) (Gilbert et al, 2004)					*ERR at 1 Gy and at attained age 60 (with 95% CI)*	*EAR per 10,000 persons per year at 1 Gy and at attained age 60 (with 95% CI)*
	Males	167 [tt]	73.5	0.21 Gy	52,546	4.7 (3.3, 6.7)	115 (81, 156)
	Females	24	3.8	0.38 Gy	17,476	19 (9.5, 39)	49 (29, 78)
13.2.2	Sellafield plutonium workers (Omar et al, 1999)	133	145.78	0.19 Sv	134,817	1.12 [uu]	
13.2.3	Los Alamos workers (Wiggs et al, 1994)	8 [vv]	n.a.	n.a.	n.a.	1.78 (90% CI 0.79, 3.99) [ww]	
13.2.5	Rocky Flats workers: lung cancer case–control study (Brown et al, 2004)	87 [xx]	n.a.	n.a.	n.a.	1.23 [yy]	
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	217	255 [l]	n.a.	n.a.	1.18 (0.97, 1.42) [zz]	
13.3.2	Oak Ridge: Y-12 plant workers (Richardson and Wing, 2006)	111	n.a.	n.a.	n.a.	<1	

TABLE 3.8 ***continued***

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e Mean dose to the affected lung.
f 95% CI here.
g Wald-type CI; likelihood-based lower confidence bound could not be identified.
h Based on patients treated for Hodgkin disease 5 or more years before diagnosis of lung cancer.
i Based on cancer incidence rates for Stockholm.
j Trend in risk with dose not statistically significantly different from zero.
k The values given exclude the period within 5 years of first treatment.
l Based on national mortality rates.
m Dose–response analysis based on the number of treatment courses given.
n Based on a dose–response analysis for irradiated patients with more than 10 years of follow-up.
o Calculated as [(obs − exp) x 10^4 / (PY x mean dose)] with Poisson-based confidence interval.
p The values given exclude the period within 10 years of exposure and ages at risk less than 20 years.
q Cases excluding those monitored for occupational exposure not more than 15 years prior to the date of death, and excluding cases among non-monitored workers.
r Cases including those monitored for occupational exposure not more than 15 years prior to the date of death, and cases among non-monitored workers.
s Dose to cases excluding that from work-related X-ray examinations.
t Dose to cases including that from work-related X-ray examinations.
u Based on a 15-year latent period.
v Mean annual effective dose.
w Based on a 10-year latent period.
x Number of cancers in both the exposed and the comparison group.
y Average cumulative dose in the exposed group, arising from internal and external exposures.
z Based on a dose–response analysis conducted solely within the exposed group.
aa See text and Table 3.9 concerning the conversion from WLM to Sv.
bb For age at exposure 30–39 years, time since exposure 15–24 years and exposure rate < 8 WL.
cc From Lubin et al (1995).
dd When compared to national rates.
ee Value from Samet et al (1991).
ff Revised value for persons in nested case–control study (Howe and Stager, 1996).
gg Values based on case–control analysis with revised exposure estimates (Howe and Stager, 1996).
hh Coefficient based on time-weighted cumulative exposure.
ii See text and Table 3.9 concerning the conversion from Bq m^{-3} to Sv.
jj Value for controls.
kk Incorporating an adjustment for year-to-year variability in radon measurements.
ll Values for controls in the Shenyang and Gansu studies, respectively.
mm Value taken from UNSCEAR (2008).
nn Relative to unexposed controls, among whom 29 cases were observed, compared with 49.6 expected.
oo Amount of Thorotrast administered.
pp Relative to comparison group.
qq Mean amount of Thorotrast administered in the first series of Japanese patients (Mori et al, 1999b).
rr Based on follow-up and deaths 5 years or more following the first examination.
ss Relative to a group of unexposed patients, among whom 1 death occurred compared with 4.8 expected.
tt Observed and expected numbers are solely for workers with plutonium doses estimated to be greater than zero.
uu Relative to other radiation workers at Sellafield; difference is not statistically significant.
vv Workers with plutonium body burden of 74 Bq or more.
ww Comparison group consists of workers with plutonium body burden below 74 Bq.
xx Among workers with a non-zero internal lung dose.
yy For the highest quartile of plutonium systemic deposition, relative to the lowest quartile. This relative risk was not statistically significantly greater than 1.
zz Relative to workers not monitored for any radionuclide.

TABLE 3.9 Suggested values for the estimated annual effective dose from radon in the UK based on the different estimates of the dose conversion coefficient for radon decay products in the domestic environment (taken from AGIR, 2009a)

Study	Dose conversion coefficient (mSv WLM^{-1})	Estimated annual effective dose at the UK mean radon concentration of 20 Bq m^{-3} (mSv)
Values based on dosimetric calculations [a]		
Hopke et al (1995)	6	0.7
Porstendorfer and Reineking (1999)	7	0.8
Marsh and Birchall (2000)	15	1.7
Kendall and Smith (2002) Type F	5	0.5
Kendall and Smith (2002) Type M	20	2.0
Values based on epidemiology [b]		
Wrixon et al (1988)	10	1.0
ICRP (1993) domestic	4	0.4
ICRP (1993) occupational	5	0.5
EPA (2003) domestic	7	0.7
EPA (2003) occupational	9	0.9
Darby et al (2005a)	4 (1–8)	0.4 (0.1–0.8)

Notes

a The two values quoted from Kendall and Smith (2002) were obtained by assuming different absorption rates from lung to blood, Type F and Type M clearance.

b The two values quoted for the epidemiological studies are the different estimates of effective dose applying at home and work, respectively.

3.10 Bone and Connective Tissue

3.10.1 General epidemiology

In the UK each year, about 1,800 new cases of bone and connective tissue cancers are diagnosed, accounting for less than 1% of all cancers (Cancer Research UK, 2008). The age-standardised incidence rate is around 3 per 100,000 persons and is somewhat higher in males than females, with the male excess being most pronounced in the 15–24 year age group and at ages of 60 years and above (Cancer Research UK, 2008). Malignant tumours of connective tissue are about three times as frequent as those of bone.

The principal types of bone cancer are osteosarcoma, chondrosarcoma and the Ewing sarcoma family of tumours (ESFT, including peripheral primitive neuroectodermal tumour). The incidence of osteosarcoma rises to a first peak in adolescence, slightly earlier in girls than boys, then returns to a lower, fairly constant

level until the age of 55 to 60 years, after which it rises steadily with age. The incidence of chondrosarcoma increases with age, while ESFT has a peak in early adolescence and is very rare after 35 years of age (Miller et al, 2006). There are many different types of connective tissue cancer, or soft tissue sarcoma, including liposarcoma, leiomyosaroma, rhabdomyosarcoma, fibrosarcoma, malignant fibrous histiocytoma (MFH) and malignant peripheral nerve sheath tumour (MPNST).

Recent advances in pathology have led to marked changes in the relative frequency with which some types of soft tissue sarcoma are diagnosed; in particular, MFH and fibrosarcoma are much less often diagnosed than formerly (Daugaard, 2004). ESFT, which used always to be classed as primary tumours of bone, are now often diagnosed in extra-osseous sites. Rhabdomyosarcoma is most frequent in early childhood, whereas the incidence of most other types increases with age (Berwick, 2006). While most soft tissue sarcomas arise in connective tissue (muscle, blood vessels, etc), substantial numbers of some types, notably leiomyosarcoma and rhabdomyosarcoma, occur in organ-specific sites (Mack, 1995).

In this report, connective tissue cancer refers only to sarcomas whose primary site is in connective tissue (muscle, blood vessels, etc), and soft tissue sarcomas of other sites are considered along with cancers of other types in the same sites. Consequently, incidence and mortality data for cancer with connective tissue as primary site are bound to underestimate the true rates for soft tissue sarcomas, with the degree of underestimation depending on how closely the site of origin is specified at diagnosis or death. Connective tissue cancers also exclude Kaposi sarcoma, which is a separate category in the ICD. It was very rare in most Western populations before the onset of the HIV/AIDS epidemic and virtually all cases are attributable to HHV-8 infection in immunosuppressed individuals (Parkin, 2006).

Several genetic syndromes are associated with increased risk of cancers of bone or connective tissue (Berwick, 2006; Miller et al, 2006). The most frequent are probably neurofibromatosis 1 (mainly MPNST, but also rhabdomyosarcoma), heritable retinoblastoma (osteosarcoma and soft-tissue sarcomas) and Li-Fraumeni syndrome (various soft-tissue sarcomas and osteosarcoma). The extreme rarity of ESFT among people of East Asian or sub-Saharan African ethnic origin strongly indicates a role for genetic predisposition in the aetiology of this group of tumours, reinforced by the finding of genetic differences between tumours from Japanese and European patients (Ozaki et al, 2002). Paget disease, which mainly affects people aged over 50 years, is a risk factor for osteosarcoma in older adults (Miller et al, 2006).

3.10.2 Findings from studies of radiation exposure

3.10.2.1 Informative studies and evidence for association and causality

Table 3.10 summarises findings from cohort and case–control studies of cancers of bone and connective tissue among radiation-exposed groups, specifically for studies in which individual assessments of exposure were made. Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the most informative studies are those of external low LET exposure among patients given radiotherapy for malignant disease, which are based on reasonably large numbers of incident cases and reliable dosimetry. For internal high LET exposure, the relative risk was not calculated in the only incidence study with more than a handful of observed cases.

Based on the epidemiological evidence from the studies listed in Table 3.10, it can be concluded that there is evidence of an association between radiation exposure and cancers of bone and connective tissue. Consistency of results and the large numbers of cases in some studies indicate that these associations are causal. The point estimates from the studies of children given radiotherapy are very close to each other. It should be noted, however, that there was some overlap of subjects between the various studies of childhood cancer survivors, all of which included children treated for retinoblastoma. Furthermore, study 2.1.3 was restricted to retinoblastoma patients and the sarcomas occurred exclusively among survivors of the heritable form of the disease, who have greatly increased susceptibility to a wide range of subsequent cancers (Fletcher et al, 2004; Kleinerman et al, 2004, 2005a). In contrast to studies 2.1.1 and 2.1.2, this study included soft tissue sarcomas as well as bone cancers. Regrettably, a more recent analysis of study 2.1.3 with extended follow-up and a considerably larger number of second cancers (Kleinerman et al, 2005b) did not include revised dose-specific estimates.

There is much less information on the risk of bone and connective tissue cancer in people who have received radiotherapy in adulthood. In an analysis of the incidence of bone and soft-tissue sarcomas among a cohort of 6,597 females treated for breast cancer, Rubino et al (2005) estimated the ERR Gy^{-1} as 0.05 [95% CI (lower bound not estimated), 1.18], based on 12 cases. The magnitude of the excesses of observed over expected cases of bone cancer in the two largest studies of internal high LET exposure, involving medical exposure to radium as treatment for tuberculosis or ankylosing spondylitis and occupational exposure of radium luminisers, is evidence that there is also an association of adult radiation exposure with bone sarcoma. The numbers of bone cancers in cohorts of Thorotrast patients have invariably been small, but the excess (based on two deaths) in the US component of the international study was statistically significant and it has been pointed out that radium-224 is a decay product of thorium-232 (Travis et al, 2003b). Two studies (13.2.1 and 13.3.1) have reported relevant mortality data for workers exposed to plutonium, but the risk estimates were based, respectively, on only three cases of bone cancer (Koshurnikova et al, 2000) and two cases of bone or connective tissue cancer (Carpenter et al, 1998) and the confidence intervals were very wide.

There is less evidence supporting an association between radiation exposure and connective tissue cancer or soft tissue sarcomas. The strength of association in study 2.1.3, together with the known susceptibility to radiation-induced cancers among survivors of heritable retinoblastoma, indicates that the association is likely to be causal. The only study specifically of connective tissue cancer following radiation exposure in adulthood failed to find any association.

The Life Span Study was the most informative study of low dose exposure because it was the only one to include exposures occurring at all ages and the only one to present risk estimates by sex, age at exposure and time since exposure. The results given in Table 3.10 are based on rather small numbers of cases, however, and risk estimates are only presented for bone and connective tissue combined. In the most recent report on cancer incidence in the Life Span Study (Preston et al, 2007), the ERR Gy^{-1} for all sarcomas combined were 0.76 (90% CI 0.08, 2.3) in males, 0.20 (90% CI 0.02, 0.80) in females and 0.49 (90% CI 0.07, 1.4) overall. These results were based on the much larger number of 149 cases, of which fewer than 40% were in bone or connective tissues. Again, results were not given separately by primary site. The results from the UK NRRW were consistent with those for adult exposure from the Life Span Study and indicated the risk was similar for bone and for connective and soft tissue (Muirhead et al, 2009).

TABLE 3.10 Risk estimates for incidence and mortality for cancer of bone and connective tissue from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Gy or more for incidence. The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007) [a]						
	Males	4	n.a. [b]	0.22	436,180	3.34 (0.90, 9.69) [c]	<0 (<0, <0) [c]
	Females	3	n.a.	0.21	729,608	<0 (<0, <0) c	<0 (<0, 9.75) [c]
	Both sexes						
	Age at exposure <20 y	3	n.a.	0.22	586,255	4.33 (0.90, 16.11) [d]	<0 (<0, <0) [d]
	20–39 y	2	n.a.	0.21	378,204	3.16 (<0, 24.05) [c]	<0 (<0, 12.66) [c]
	40+ y	2	n.a.	0.20	201,330	<0 (<0, <0) [e]	<0 (<0, <0) [e]
	Time since exposure						
	12–15 y	3	n.a.	0.24	634,356	1.27 (0.07, 4.55)	<0 (<0, 10.87)
	15–30 y	4	n.a.	0.23	531,433	2.28 (0.23, 9.32)	<0 (<0, 18.77)
	>30 y	7	n.a.	0.23	1,165,788	1.64 (0.40, 4.31)	<0 (<0, 14.36)
2.1.1	Childhood radiotherapy, international (bone) (Tucker et al, 1987)	54 [f]	n.a.	27	n.a.	0.06	n.a.
2.1.2	Childhood cancer – UK (bone) [g] (Hawkins et al, 1996)	49 [g]	18.8 [g]	10 [h]	n.a.	0.16 (0.07, 0.37) [f,g,i]	n.a.
2.1.3	Retinoblastoma patients (bone and soft tissue sarcoma) [j] (Wong et al, 1997)	81	n.a.	20.0 (cases) 32.8 (controls)	n.a.	0.19 (0.14, 0.32) [i]	n.a.
2.2.3	Cervical cancer case–control (connective tissue only) [k] (Boice et al, 1988)	42	63 [l]	7.0	n.a.	−0.05 (−0.11, 0.13) [m]	−0.01 (−0.03, 0.03) [n]

TABLE 3.10 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)						
	Bone	17	n.a.	0.025	2,388,848	1.18 (<–1.93, 36.3)	n.a.
	Connective and soft tissue	58	n.a.	0.025	2,388,848	<–1.93 (<–1.93, 0.3)	n.a.
Mortality							
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)						
	Bone	16	n.a.	0.0194	5,192,710	<0	n.a.
	Connective tissue	39	n.a.	0.0194	5,192,710	0.32 (<0, 11.5)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)						
	Bone	8	n.a.	0.025	2,433,573	<–1.93 (<–1.93, 12.1)	n.a.
	Connective and soft tissue	31	n.a.	0.025	2,433,573	<–1.93 (<–1.93, 4.76)	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)	Excess absolute risk per 10,000 persons per year
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
11.1	Radium-224 TB and ankylosing spondylitis patients (bone) (Nekolla et al, 1999, 2000)	56	0.3	30.6 Gy	n.a.	0.17 [o]	0.9 j
11.2	Radium-224 ankylosing spondylitis patients (bone and connective tissue) (Wick et al, 1999)	4	1.3	~6 Gy	32,800	4.3 [p]	n.a.

TABLE 3.10 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)	Excess absolute risk per 10,000 persons per year
Mortality							
12.1	German Thorotrast patients (bone sarcoma) (van Kaick et al, 1999; Becker et al, 2008)	7 males 3 females	n.a.	20.6 ml [q]	n.a.	Males: 2.5 (0.6, 15.3) Females: 3.0 (0.2, 158) [r]	n.a.
12.3	Portuguese Thorotrast patients (bone) (dos Santos Silva et al, 2003) [s]	5	0.39 [t]	20 ml [q] (median)	13,283	7.60 (0.85, 359) [u]	n.a
13.1.1	US radium luminisers (bone) (Stebbings et al, 1984, 1989; Rowland, 1994; Stehney, 1994) [v]	46	<1 [u]	8.6 Gy [u]	35,819 [u]	n.a.	~13 [u]
13.2.1	Mayak plutonium workers (bone) (Koshurnikova et al, 2000; Sokolnikov et al, 2008)	6	n.a.	n.a.	84,593	Males: 0.8 (<0, 5.2) Females: 3.4 (0.4, 5.2) [w]	n.a.
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	2	2.0 [s]	n.a.	n.a.	1.01 (0.12, 7.35) [x]	n.a.

Notes

a Values taken from UNSCEAR (2008).
b Not available.
c Value applies at attained age 70 years following exposure at age 30 years.
d Value applies at attained age 70 years following exposure at age 10 years.
e Value applies at attained age 70 years following exposure at age 50 years.
f Those with doses less than 10 Gy.
g Results are based in a case–control analysis of bone cancer.
h Value taken from UNSCEAR (2008), Table 30.
i 95% CI here.
j Results are for patients with bone or soft tissue sarcoma for whom dosimetry information was available, based on an earlier follow-up.
k Excess absolute risk computed using baseline incidence data derived from the cohort study of Boice et al (1985).
l Calculated as the ratio of the observed cases to the estimated relative risk.
m Estimated based on 10-year survivors.
n Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
o Approximate value based on exposure at age 30.
p Relative to unexposed controls, among whom 1 case was observed, compared with 1.4 expected.
q Amount of Thorotrast administered.
r Crude relative risk, based on one case in the control group. This relative risk is not significantly different from 1 ($p > 0.05$).
s Based on follow-up and deaths 5 years or more following the first examination.
t Based on national mortality rates.
u Relative to a group of unexposed patients, among whom 1 death occurred compared with 0.60 expected.
v Values taken from UNSCEAR (2008).
w Excess relative risk per Gy.
x Relative to workers not monitored for any radionuclide.

3.10.2.2 Estimates of radiation risks

The studies of childhood cancer patients consistently indicate that the risk of bone and connective tissue cancer increases with increasing level of external radiation dose. The best estimate is that of study 2.1.3 (Wong et al, 1997), namely an ERR of 0.19 (95% CI 0.14, 0.32) at 1 Sv, because this study was the largest one to include both types of cancer and its risk estimate also had the narrowest confidence interval. Some studies (Tucker et al, 1987; Hawkins et al, 1996) found a decline in risk at the highest dose level, possibly because of a cell killing effect. Such an effect might also contribute to the null result in the study of females who received radiotherapy for cervical cancer (Boice et al, 1988).

For internal exposure, all of the studies that gave a confidence interval for the risk were based on small numbers of exposed cases. Only the German and Portuguese Thorotrast studies reported a mean dose, but dose-specific risks were not estimated in either study. The German study is more informative because it is based on larger numbers of cases and provides estimates separately for males and females. The relative risks for the two sexes were similar and, though lower than the relative risk in the Portuguese study, were consistent with it because all of the confidence intervals were very wide. The Mayak workers study, 13.2.1, indicated an increasing risk of bone cancer with increasing plutonium body burden, but this was based on only three deaths in the most highly exposed group (Koshurnikova et al, 2000).

3.10.2.3 Modifying factors

There is some information on how radiation risks might be modified by other factors. The evidence relating to age is incomplete. The risk estimates for the studies of cancer following radiotherapy in childhood are consistent with each other, and much higher than that for the single study to investigate the risk of bone or connective tissue cancer following radiotherapy in adulthood. In the US study of retinoblastoma survivors the ERR per unit dose did not vary with age at exposure (Wong et al, 1997), though that study has consistently found a higher incidence of sarcoma among those who were irradiated during the first year of life (Wong et al, 1997; Abramson and Frank, 1998). The most informative study on low dose exposures, the Life Span Study, gave significantly higher ERR values for persons exposed in the first 20 years of life than for those aged over 40 years at exposure.

In the results from the Life Span Study presented in Table 3.10, the ERR was lower for females than for males. In the most recent analysis of the Life Span Study, the ERR and EAR for sarcomas of all sites combined were both lower for females than for males, and the difference was significant for the EAR (Preston et al, 2007). The latter results are impossible to interpret in relation to bone and connective tissue cancers, however, since more than 60% of the relevant cancers were soft-tissue sarcomas of specific organs. Study 2.1.3 found no difference in risk between male and female retinoblastoma patients (Wong et al, 1997). While it is well known that survivors of heritable retinoblastoma are at enormously increased absolute risk of subsequent sarcomas, two studies provide evidence that their radiation-associated relative risk does not differ from that of other childhood cancer patients (Tucker et al, 1987; Hawkins et al, 1996).

3.10.2.4 Gaps in knowledge

There is little information on the effect of low dose external exposure, consistent with the low incidence of bone and connective tissue cancer in all population groups. As with virtually all cancer sites other than the thyroid, there is no information at all on the effect of internal exposure in childhood.

3.11 Melanoma of Skin

3.11.1 General epidemiology

Malignant melanoma (melanoma) of the skin is relatively rare but the most lethal form of skin cancer, occurring most commonly in fair-skinned individuals living in sunny locations. The highest incidence rates are reported from Australia and New Zealand, North America and Northern Europe (Parkin et al, 2005; Gruber and Armstrong, 2006). In Europe, melanoma is the 17th most commonly diagnosed cancer in males and the eighth most common cancer in females (de Vries et al, 2004). In the UK, reporting of skin malignancies, both melanocytic and non-melanocytic, to cancer registries has improved in recent years, but variability still exists among different registries in methods and completeness of case ascertainment (Goodwin et al, 2003). The incidence of melanoma has been rising in Europe and other countries, partially due to improved reporting and early detection (de Vries et al, 2004; Downing et al, 2006). Exposure to solar ultraviolet radiation (UVR) is the major cause of skin melanoma.

As with non-melanoma skin cancer (see Section 3.12), exposure to solar UVR is the major cause of melanoma. The anatomical distribution of melanoma differs somewhat from that of non-melanoma skin cancer. Melanoma arises in different body sites for males and females. The trunk (back, abdomen and chest) is the most common location for males, whereas the legs, especially the lower legs, are the most common site for females (Gruber and Armstrong, 2006). This distribution is consistent with the notion that intermittent, rather than continuous, sunlight exposure is associated with melanoma.

Nevi are a well-established risk factor and also can be a precursor lesion for melanoma. The host risk factors include such pigmentary characteristics as fair skin, blond or red hair, blue eyes and the presence of freckles. Familial aggregation has been documented for melanoma and, in addition, several specific genetic syndromes have been associated with melanoma, including *xeroderma pigmentosum*, Bloom syndrome, Werner syndrome, Li-Fraumeni syndrome and, more recently, familial atypical mole-malignant melanoma (Gruber and Armstrong, 2006).

3.11.2 Findings from studies of radiation exposure

3.11.2.1 Informative studies and evidence for association and causality

Table 3.11 summarises skin melanoma risk data from those cohort studies of populations exposed to ionising radiation for which individual dose estimates are available. In addition, a number of studies of cancer patients treated with radiotherapy have shown a higher than expected number of deaths from skin melanoma following high dose cancer radiotherapy (Olsen et al, 1993; Wong et al, 1997; van Leeuwen et al, 2000). Difficulties arise in interpreting these data, most importantly due to the lack of dose–response analyses and possibly confounding by surveillance bias, effects of chemotherapy and underlying genetic susceptibility in certain cancer patients (Shore, 2001). However, a more recent case–control study nested in a combined Nordic, French and British cohort of childhood cancer survivors (Table 3.11 and Guérin et al, 2003) demonstrated an odds ratio (relative risk) for melanoma increasing significantly with increasing local radiation doses estimated. There thus is suggestive evidence of increased skin melanoma after exposure to low LET exposure at the high dose levels given for radiotherapy.

TABLE 3.11 Risk estimates for incidence and mortality for melanoma of skin from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.01 Gy or more for incidence. The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 95% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 95% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–87 (Thompson et al, 1994)						
	Male	3	n.a. [a]	0.36 [b]	297,454 [b]	1.24 (<0, 9.34)	0.04 (<0, 0.32)
	Female	3	n.a.	0.35 [b]	491,130 [b]	−0.18 (<−0.18, 3.44)	−0.02 (<−0.02, 0.32)
	Age at exposure <20 y	1	n.a.	0.35 [b]	363,292 [b]	0.16 (<0, 13.22)	0.02 (<0, 0.21)
	>20 y	5	n.a.	0.36 [b]	425,292 [b]	0.26 (<0, 3.80)	0.00 (<0, 0.24)
	All	6	n.a.	0.35	788,584	0.19 (<0, 3.00)	0.00 (<0, 0.13)
	(Preston et al, 2007)						
	All	13	n.a.	n.a.	1,165,788	n.a.	n.a.
2.1.4	Combined Nordic, French and British childhood cancer survivors (Guérin et al, 2003)	16	n.a.	>15 Gy local dose	n.a.	RR = 13 (0.94, 174) at >15 Gy local dose	n.a.
6.4	Canadian National Dose Registry (Sont et al, 2001)	222	191.3	0.0066	2,667,903	4.3 (<0, 19.6) [c]	n.a.
Mortality							
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	87	n.a.	0.0194	5,192,710	0.15 (<0, 5.44) [c]	n.a.
EXTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES							
Mortality							
A7.1	European aircraft cockpit crew (Langner et al, 2004)	14	9.91	0.002–0.005	336,413	n.a.	n.a.

Notes

a Not available.

b Values taken from UNSCEAR (2008).

c 90% CI here.

Much less information is available on melanoma risk at low to moderate low LET radiation doses, and the available data are inconsistent. There are too few cases of melanoma in the Life Span Study to allow detailed risk assessment (Table 3.11 and Ron et al, 1998). No significant association has been found for melanoma and radiation exposure in large cohort studies of nuclear industry workers in Canada, the USA, UK and elsewhere (Cardis et al, 1995, 2007; Sont et al, 2001). A possible association between low LET radiation exposure and skin melanoma has been suggested by an increased relative risk of melanoma – adjusted for sunlight exposure – among US radiological technologists who worked before 1950, when radiation exposure was high (Freedman et al, 2003); this analysis did not include radiation dose estimates. Thus the available evidence is inconclusive for establishing a causal association between exposure to low LET radiation at low to moderate doses and skin melanoma.

Airline pilots and flight personnel can be exposed to doses as high as 6 mSv per year with a substantial (up to 60%) neutron component (McAuley et al, 1996; IARC, 2000). The causal nature for the increased risk of skin melanoma reported from cohort studies of flight crew in North America (Band et al, 1990, 1996; Nicholas et al, 1998), Japan (Kaji et al, 1993) and European countries (Gundestrup et al, 1999; Irvine et al, 1999; Milanov et al, 1999; Haldrosen et al, 2000; Rafnsson et al, 2000; Ballard et al, 2002; Hammer et al, 2002; Pukkala et al, 2002; Zeeb et al, 2002; Paridou et al, 2003) remains unclear because of reliance upon standardised incidence ratios only without internal comparison, lack of radiation dose estimates and the inability to consider confounding effects of UVR exposure in these studies. A large combined study by Langner et al (2004) of cohorts of airline pilots from nine European countries (Denmark, Finland, Germany, Great Britain, Greece, Iceland, Italy, Norway and Sweden) indeed found no association between skin melanoma and cumulative dose (mean estimated annual doses in the range 2–5 mSv and cumulative lifetime doses not exceeding 80 mSv). It can be concluded that there is no established causal association between exposure to cosmic radiations and skin melanoma.

3.11.2.2 Gaps in knowledge

While there is suggestive evidence linking high dose radiotherapy to skin melanoma, definitive studies, such as dose–response analyses, are needed to establish causality. In view of the suggestion of an increase in melanoma risk among US radiological technologists, dose–response data are also needed regarding melanoma risk in relation to external exposure to low LET radiation at low to moderate doses. Since skin melanoma is rare, combined or pooled analyses of various exposed populations would be informative.

3.12 Non-melanoma Skin

3.12.1 General epidemiology

Non-melanoma (or non-melanocytic) skin cancer is rarely fatal but is among the most common cancers in fair-skinned populations living in sunny locations. The highest rates are reported from Australia and the lowest from Finland (English et al, 1997; Karagas et al, 2006). Non-melanoma skin cancer incidence rates in the UK are lower than those in sunnier climates (Harvey et al, 1996), although differences in registrations in different countries could be a factor. Basal cell carcinomas are the most common malignancy in fair-skinned populations, comprising about 70–80% of the non-melanomas in males and 80–90% in females (Karagas et al, 2006). Exposure to solar ultraviolet radiation (UVR) is the dominant cause of non-melanoma cancer of the skin (IARC, 1992). Both basal cell and squamous cell carcinomas

occur predominantly in the sunlight-exposed parts of the body, ie the face, head, and neck; lifetime sun exposure as well as recreational and occupational sun exposure have been linked to squamous cell carcinoma, while intermittent or intense sun exposure in addition to sun exposure during childhood or teenage years may be more specifically related to basal cell carcinoma (Armstrong et al, 2001; Karagas et al, 2006).

Other risk factors include immunosuppression, as exemplified by the increased risk of skin cancer – especially squamous cell carcinoma – among organ transplant recipients (Hartevelt et al, 1990), and occupational exposure to or oral intake of arsenic (IARC, 1980). Individuals with a rare recessive genetic disorder, *xeroderma pigmentosum*, have an exceedingly high risk of developing skin cancer early in life (Kraemer et al, 1987) due to deficiency in nucleotide excision repair for UVR-induced DNA damage. Basal cell nevus syndrome, a rare dominant genetic condition involving mutated PTCH gene, predisposes the carrier to a very high risk of basal cell carcinoma of the skin (Gorlin, 1987), and patients with basal cell nevus syndrome are exquisitely sensitive to the carcinogenic effect of ionising radiation (ICRP, 1998).

3.12.2 Findings from studies of radiation exposure

3.12.2.1 Informative studies and evidence for association and causality

Table 3.12 provides data from cohorts exposed to ionising radiation for which non-melanoma incidence data and individual radiation dose estimates are available. Because non-melanoma skin cancers are rarely fatal, mortality data are a poor measure of the risk. However, as briefly discussed later in this section, some useful insights can be obtained from skin cancer mortality, especially from historical cohort studies carried out when incidence data were not available. In addition to the cohort data, a few case–control studies are informative (Karagas et al, 1996; Gallagher et al, 2000; Lichter et al, 2000). Few studies of second cancers following cancer radiotherapy have reported on non-melanoma skin cancer risk, and the two most informative of these, concerning Stanford Hodgkin lymphoma patients (Wolden et al, 1998) and Danish child/adolescent cancer patients (Olsen et al, 1993), do not distinguish between risks related to radiation and non-radiation treatment (Shore, 2001). In contrast, there is no significantly increased risk of non-melanoma skin cancer in studies of patients irradiated at adult ages for acute post-partum mastitis or tuberculosis (Shore et al, 1990) (Table 3.12). These cohorts were also exposed at moderate radiation doses, roughly comparable to those in the studies of childhood irradiation that are described above.

Evidence of a causal association between exposure to low LET radiation at low to moderate doses and basal cell carcinoma is provided by dose–response relationships demonstrated by many exposed populations: patients medically irradiated for non-malignant diseases, such as tinea capitis (Ron et al, 1991; Shore et al, 2002), enlarged thymus (Hildreth et al, 1985; Shore et al, 1990), and tonsillitis in infancy or in early childhood (Schneider et al, 1985; Shore et al, 1990); also the Life Span Study cohort of Japanese atomic bomb survivors (Ron et al, 1998) and the UK NRRW (Muirhead et al, 2009). The lack of a demonstrated risk of basal cell carcinoma of the skin associated with radiotherapy given during adult years (as in the post-mastitis, TB fluoroscopy findings shown in Table 3.12) (Shore et al, 1990) is consistent with the inverse relationship between age at exposure and radiation risk, as discussed below (Ron et al, 1998).

No increased radiation-related risk of squamous cell carcinoma of the skin has been demonstrated in any of the medically exposed populations or the Japanese atomic bomb survivors. However, excess mortality

from skin cancer found in very early radiologists in the UK (Smith and Doll, 1981) and the USA (Matanoski et al, 1975), and more recently in Chinese X-ray workers (Wang et al, 2002), suggests an association between repeated exposures to excessively high dose X-irradiation and squamous cell carcinoma, which is more fatal than basal cell carcinoma. This is supported by results from a case–control study in New Hampshire in the USA, which indicated a significantly increased relative risk of squamous cell as well as basal cell carcinoma of the skin following radiotherapy (Lichter et al, 2000), although the possibility of confounding by other treatment cannot be rejected. It is concluded that there is suggestive evidence that squamous cell carcinoma may result from high dose radiation exposure.

For external high LET radiation exposure, a pooled analysis of national cohorts of airline pilots from Denmark, Finland, Iceland, Norway and Sweden (Pukkala et al, 2002) demonstrated a significantly higher than expected incidence for basal cell carcinoma and other non-melanoma skin cancer. However, no significant dose response was found and the possible confounding effect of recreational UVR exposure was not addressed. No causal association can be concluded.

3.12.2.2 Estimates of radiation risks

For external low LET radiation exposure, the best estimate of radiation-related risk for non-melanoma skin cancer is given by the latest incidence among the Life Span Study cohort. The estimated ERR at age 70 years after exposure at age 30 for doses above 1 Gy is 1.2 (90% CI 0.57, 2.3). For basal cell carcinoma a linear excess relative risk model predicts an ERR at 1 Sv of 1.8 (90% CI 0.83, 3.3) (Ron et al, 1998). The Life Span Study dose–response data for basal cell carcinoma of the skin are suggestive of a non-linearity and uncertainty at doses below 1 Sv.

3.12.2.3 Modifying factors

There is strong evidence from the Life Span Study incidence data that the ERR for basal cell carcinoma is modified by age at exposure. The ERR decreases significantly with increasing age at exposure (Ron et al, 1998). Epidemiological evidence is rather inconsistent regarding the nature of joint effects of UVR and low LET radiation exposure. The Life Span Study data show that the EAR for a unit skin surface (per m^2 per 10^5 person-years per Sv) does not differ for tumours in the UVR-exposed body sites when compared with UVR-shielded sites (Kishikawa et al, 2005), suggesting a uniform distribution of EARs over the body regardless of UVR exposure. However, New York tinea capitis data (Shore et al, 2002) show the excess risk per unit dose and unit skin area to be significantly higher for the UVR-exposed margin of the scalp than for the relatively UVR-shielded scalp. Comparison of the results regarding the nature of the interaction between UVR and ionising radiation from the Japanese and US populations is complicated by the difference in pigmentary characteristics in the two populations.

3.12.2.4 Gaps in knowledge

There is uncertainty in the shape of the dose response for basal cell carcinoma for low LET radiation exposure at low doses, ie less than 1 Gy. There is little information on the risk of squamous cell carcinoma of the skin at doses below levels used for cancer radiotherapy. There is little information on how the radiation-related risk of non-melanoma skin cancer, either basal cell or squamous cell carcinoma, is modified by UVR exposure. Whether a radiation-related risk of non-melanoma skin cancer is modified by genetic factors (genetic susceptibility) is a relevant question for non-melanoma skin cancer because of the known radiosensitivity of basal cell nevus syndrome patients.

TABLE 3.12 Risk estimates for non-melanoma skin cancer incidence from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with weighted skin doses (shielded kerma) of 0.005 Sv or more. The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	66	n.a. [a]	0.22	436,180	0.10 (0.002, 0.41) [b]	0.38 (0.03, 1.3) [b]
	Females	101	n.a.	0.21	729,608	0.23 (0.005, 0.75) [b]	0.32 (0.03, 1.0) [b]
	Both sexes						
	Age at exposure <20 y	41	n.a.	0.22	586,255	2.28 (0.04, 7.8) [c]	2.3 (0.2, 7) [c]
	20–39 y	67	n.a.	0.21	378,204	0.17 (0.003, 0.55) [b]	0.35 (0.03, 1.1) [b]
	40+ y	59	n.a.	0.20	201,330	0.01 (0.00, 0.08) [d]	0.05 (0.00, 0.29) [d]
	All	167	n.a.	0.21	1,165,788	0.17 (0.003, 0.55) [b]	0.35 (0.03, 1.1) [b]
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	326	n.a.	0.025	2,388,848	1.50 (0.23, 3.4)	n.a.
Childhood exposure only							
3.1.1	New York tinea capitis (whites) (BCC [e]) (Shore et al, 2002)	124	37.7	4.3	54,049	0.6 (0.3, 1.1) [f]	1.9 (0.5, 3.3) [f]
3.1.2	Israel tinea capitis (BCC) (Ron et al, 1991)	42	10.0	6.8	265,070	0.70 (0.35, 1.32) [g]	1.31 (0.94, 1.77) [e]
3.1.3	Rochester thymic irradiation (BCC, SCC [h]) (Hildreth et al, 1985; Shore, 1990)	14	4.2	2.3	87,000	1.05 (0.50, 1.9)	0.50 (0.3, 0.9)
3.1.4	Tonsil irradiation (BCC, SCC) (Schneider et al, 1985; Shore, 1990)	63	45.0	3.8	96,000	0.11 (0.03, 0.19)	0.50 (0.2, 1.0)

TABLE 3.12 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
Adult exposure only							
3.2.3	New York acute post-partum mastitis (BCC, SCC) (Shore, 1990)	14	10.7	2.6	14,000	0.12 (0, 0.8)	0.90 (0, 2.8)
4.1	Massachusetts TB fluoroscopy (BCC, SCC) (Shore, 1990)	80	75.3	9.6	122,000	0.01 (0, 0.03)	0.04 (0, 0.2)

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
EXTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
7.3	Nordic airline pilots (Pukkala et al, 2002)			11% exceeding 0.02 Sv	177,243	
	BCC	61	24.8			1.86 (0.98, 3.54) [i]
	Non-BCC	27	13.0			1.92 (0.74, 4.98) [g]
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	14	9.3	n.a.	25,480	1.3 (0.6, 2.8) [j]

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e Basel cell carcinoma.
f 95% CI here.
g Poisson-based confidence interval.
h Squamous cell carcinoma.
i Based on comparing those with a cumulative dose >0.02 Sv with those having a cumulative dose < 0.003 Sv.
j Relative to an unexposed comparison group.

3.13 Breast

3.13.1 General epidemiology

Breast cancer is the most common cancer diagnosed and the second most common cause of cancer mortality in females in the UK. Age-standardised incidence rates have increased from 74 in 1975 to 120 in 2003 per 100,000 women, whilst the age-standardised mortality rates, which were also increasing, have now been steadily decreasing since 1989 from 41 to 28 per 100,000 women in 2004 (Cancer Research UK, 2008). The decrease in mortality rates is largely due to a combination of improved treatment and the introduction of mammography screening, whilst the increase in incidence rates is likely to be due to a number of causes, including females having fewer pregnancies and at older ages, use of hormonal contraception and hormonal therapy, and increasing obesity. Most breast cancers are adenocarcinomas originating from either ductal or lobular glandular tissue.

3.13.2 Findings from studies of radiation exposure

3.13.2.1 Informative studies and evidence for association and causality

Table 3.13 summarises findings from cohort and case–control studies of breast cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the most informative studies regarding radiation exposure and breast cancer are the eight cohort studies – including the Life Span Study of Japanese atomic bomb survivors and studies of therapeutic and diagnostic medical exposures for benign conditions – that were included in the pooled analysis by Preston et al (2002a). This pooled analysis includes females exposed to a wide range of radiation doses at different ages.

Based on the epidemiological evidence from the studies listed in Table 3.13 and the other studies mentioned above, it can be concluded that there is definitive evidence of an association between radiation exposure and female breast cancer. Furthermore, taking account of the consistency of findings across studies and the dose–response relationship found, it can be concluded that this association is causal. However, there is heterogeneity between the studies with respect to the magnitude of the excess risk which cannot be entirely explained by the strong effect of attained age (see below) and may be due to varying exposures to other modifying factors. The effects of potential modifying factors are not currently well understood, as described below.

3.13.2.2 Estimates of radiation risks

The pooled analysis of cohort studies by Preston et al (2002a) indicates that rates of female breast cancer increase with increasing level of radiation dose, and the relative risk decreases with increasing attained age. The magnitude of the risk at young ages (below the age of 20 years), however, makes the breast one of the most radiosensitive tissues. The evidence arises from persons who received both high and low doses of radiation, and the excess risk increases linearly with dose with a downturn at very high doses. In Hodgkin lymphoma survivors who were treated before age 25 years with a chest radiation dose of at least 40 Gy (without alkylating agents), the estimated cumulative absolute risks of breast cancer by age 35, 45 and 55 years were 1.4% (95% CI 0.9, 2.1), 11.1% (95% CI 7.4, 16.3), and 29.0% (95% CI 20.2, 40.1), respectively (Travis et al, 2005a).

TABLE 3.13 Risk estimates for breast cancer incidence and mortality in females from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted breast dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–90 (Land et al, 2003)	976 (714) [a]	n.a. [b]	n.a.	n.a.	1.83 (1.43, 2.28)	n.a.
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Age at exposure [c] <20 y	246	n.a.	0.22	n.a.	0.86 (0.47, 1.5) [d]	23 (15, 34) [d]
	20–39 y	222	n.a.	0.21	n.a.	0.87 (0.55, 1.3) [e]	9.2 (6.8, 12) [e]
	40+ y	59	n.a.	0.20	n.a.	0.87 (0.44, 1.5) [f]	3.7 (2.1, 5.9) [f]
	All ages	527	n.a.	0.21	729,608	0.87 (0.55, 1.3) [e]	9.2 (6.8, 12) [e]
	Attained ages 0–50 with adjustment for early-onset breast cancer	n.a.	n.a.	n.a.	n.a.	0.98 (0.64, 1.40)	5.3 (2.5, 8.6) [g]
2.1.4	Childhood cancers (France/UK) [h] (Guibout et al, 2005)	13				0.13 (<0, 0.75) [i]	n.a.
2.1.5	Childhood Hodgkin disease [h] (Bhatia et al, 1996)	17	0.2	20	n.a.	n.a. [j]	n.a.
2.2.3	Cervical cancer case– control [k] (Boice et al, 1988)	838	952 [l]	0.31	n.a.	0.03 (–0.87, 1.29) [m]	0.54 (–14.6, 21.7) [n]
	Without ovaries	91	68.4	0.31	n.a.	0.33 (–0.4, 1.8)	n.a.
2.2.5	US contralateral breast cancer (Boice et al, 1992)	655	550.4	2.82	n.a.	0.07 (<–0.1, 0.2)	n.a.
2.2.6	Danish contralateral breast cancer (Storm et al, 1992)	529	508.7	2.51	n.a.	0.02 (<–0.1, 0.2)	n.a.

TABLE 3.13 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
2.2.10	Breast cancer following Hodgkin disease (international) (Travis et al, 2003a, 2005a)	90 [o]	n.a.	21.1 [p]	n.a.	0.15 (0.04, 0.73) [i,q]	n.a.
2.2.11	Breast cancer following Hodgkin disease (USA) (Hancock et al, 1993)	25	6.1	~44.0	8832	0.07 (0.04, 0.11)	0.49 (0.29, 0.74)
3.1.3	Rochester thymic irradiation [h] (Hildreth et al, 1989)	22	7.8	0.76	38,200	2.39 (1.2, 4.0)	4.89 (2.4, 8.1)
3.1.8, 3.1.9	Swedish pooled skin haemangioma [h] (Lundell et al, 1999)	245	204	0.33	600,000	0.35 (0.18, 0.59) [i]	1.4 (0.8, 2.3) [i]
3.2.4	Swedish benign breast disease (Mattsson et al, 1993, 1995)	115	28.8	8.46	37,400	0.65 [r]	6.34 [s]
3.3.2	New York acute post-partum mastitis (Shore et al, 1986)	54	20.8	3.7	9,800	0.43 (0.3, 0.6)	9.14 (6.0, 13)
4.1	Massachusetts TB fluoroscopy (Boice et al, 1991)	142	107.6	0.79	54,600	0.40 (0.14, 0.70) [i]	7.97 (2.78, 13.8) [i]
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	151	n.a.	0.025	n.a.	−0.23 (<−1.93, 14.5)	n.a.
–	Pooled analysis of 8 cohorts (Preston et al, 2002a)	903 [t]	n.a.	0.3–5.8	996,150 [s]	0.86 (0.7, 1.04) [i]	13.4 (9.5, 17) [i]
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)	173	n.a.	0.22	1,061,690	0.79 (0.29, 1.5)	1.6 (1.2, 2.2)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994)	42 [u]	39.2 [v]	0.59 Gy	61,619	0.08 (−0.30, 0.65) [i]	0.77 (−2.45, 4.83) [i,w]
3.3.2	Peptic ulcer (Carr et al, 2002)	14	7.73 [v]	0.2	n.a.	0.1 (<0, 10.4) [i,x]	n.a.

TABLE 3.13 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
4.3	Canadian TB fluoroscopy (Howe and McLaughlin, 1996)	349	237	0.89	411,706	0.90 (0.55, 1.39) [i,y]	3.16 (1.97, 4.78) [i,z]
4.4	Scoliosis patients [h] (Doody et al, 2000)	70	35.7	0.11	184,508	2.7 (−0.2, 9.3) [i]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	103	n.a.	0.0194	n.a.	<0	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	56	n.a.	0.025	n.a.	2.28 (<−1.93, 30.37)	n.a.
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
8.5	French, Italian and Swedish iodine-131 thyroid cancer patients (Rubino et al, 2003)	54	45	6 GBq [aa]	n.a.	−0.01 per GBq (n.a., 0.04) [i]	n.a.
Mortality							
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	61 [bb]	n.a.	0.634 [cc]	n.a.	1.09 (−0.05, 15.8) [i,dd]	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
	INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES					
Incidence						
11.1	Radium-224 TB and ankylosing spondylitis patients (Nekolla et al, 1999)	28	8	~0.1 Gy [ee]	n.a.	1.9 [ff]
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	27	15.8	n.a.	12,247	1.6 (0.9, 2.8) [gg]

TABLE 3.13 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	9	n.a.	20.6 ml [hh]	n.a.	0.7 (CI 0.3, 1.6)
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	5	4.3 [v]	n.a.	n.a.	2.17 (0.63, 6.70) [ii]

Notes

a Cases identified under the tumour registry incidence study rule. Number with DS86 doses in brackets.
b Not available.
c Values taken from UNSCEAR (2008), Table 33.
d Value applies at attained age 70 years following exposure at age 10 years.
e Value applies at attained age 70 years following exposure at age 30 years.
f Value applies at attained age 70 years following exposure at age 50 years.
g Attained age > 50 years with menopause effect in the model.
h Population exposed as children.
i 95% CI here.
j Relative risks were 5.9 (95% CI 1.2, 30.3) at 20–40 Gy and 23.7 (95% CI 3.7, 152) at more than 40 Gy, relative to those with doses to the mantle region of radiotherapy of less than 20 Gy.
k Excess absolute risk among cervical cancer patients is computed using baseline incidence data derived from the cohort study (Boice et al, 1985).
l Calculated as the ratio of the observed cases to the estimated relative risk.
m Estimated based on 10-year survivors.
n Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
o Based on those exposed to at least 4 Gy.
p Value for controls.
q Based on those treated solely with radiotherapy.
r Based on a dose–response model with a component for cell killing, and evaluated for exposure at age 40 years.
s Based on a dose–response model with a component for cell killing, and evaluated for exposure at age 40 years and attained age 65 years. Value expressed in terms of breast-years, rather than person-years .
t For doses <0.01.
u Cases more than 5 years following exposure
v Based on national mortality rates.
w Calculated as [(obs − exp) x 10^4 / (PY x mean dose)] with Poisson-based confidence intervals.
x Based on patients with more than 10 years of follow-up and dividing the overall ERR (and 95% CI) by the average dose.
y Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply to exposure at age 15 years.
z Including a factor to allow for differences between Nova Scotia and other Canadian provinces. Values apply 20 years following exposure at age 15 years.
aa Mean cumulative iodine-131 activity.
bb Number of cancers in both the exposed and the comparison group.
cc Average cumulative dose in the exposed group, arising from internal and external exposures.
dd Based on a dose–response analysis conducted solely within the exposed group.
ee High LET breast dose from radium-224.
ff Relative risk at 1 Sv.
gg Relative to an unexposed comparison group.
hh Amount of Thorotrast administered.
ii Relative to workers not monitored for any radionuclide.

For external radiation, the best estimate of risk in relation to radiation exposure is that based on the pooled analysis by Preston et al (2002a), namely an ERR of 0.74 (95% CI 0.4, 1.2) at an attained age of 50 years. This estimate was based on three of the eight cohort studies, all of which were conducted in the USA (two TB fluoroscopy studies and the study of thymic irradiation). The estimates from the other five cohorts were heterogeneous. If an EAR model was used instead of an ERR model, then it would have been possible also to include the data from the Life Span Study. Preston et al concluded that there is no single simple risk model that adequately describes the radiation risks in all eight cohorts that they considered.

There is limited evidence on the effect of internal radiation exposures on breast cancer risk.

3.13.2.3 Modifying factors

After taking in to account the decrease in ERR with attained age, there is no evidence of an additional modifying effect of age at exposure (Preston et al, 2002a, 2007). There is limited information on how radiation risks might be modified by other known risk factors, such as reproductive history (Ronckers et al, 2005). Because BRCA genes are associated with DNA repair, a number of studies have evaluated whether the relative risk of radiation-induced breast cancer may be higher for females who are carriers of these mutations. Findings have been inconsistent. Females with benign breast disease may have a higher relative risk of radiation-induced breast cancer than the general population (Preston et al, 2002a). It is unclear whether this is due to the benign breast disease itself or due to the causes of benign breast disease.

3.13.2.4 Gaps in knowledge

The magnitude of the excess risk is somewhat uncertain because of the heterogeneity between the studies found in the pooled analysis by Preston et al (2002a). More information on the modifying effects of exposure to other risk factors may help to explain some of this heterogeneity. There is limited information on the effect of internal radiation exposures and on the risk of male breast cancer following radiation exposure (Ron et al, 2005).

3.14 Uterine Cervix

3.14.1 General epidemiology

Only invasive cancer is considered here. Both squamous carcinomas and adenocarcinomas occur, but the former are much more common than the latter. Incidence rates and mortality rates for cervical cancer have shown a steady decline in England and Wales since 1990, such that in 2002 there were only 2,469 new cases of cervical cancer and in 2004 there were only 957 deaths from the disease (ONS, 2008). Most, if not all, of the decline can be attributed to the success of the national cervical screening programme.

The underlying cause of cervical cancer is infection with one or more of the oncogenic subtypes of the human papilloma virus (HPV) acquired during sexual intercourse. It follows that key risk factors for the disease include early age at first intercourse and multiple sexual partners (both for the woman and for her partners).

TABLE 3.14 Risk estimates for cervical cancer incidence and mortality from studies of radiation exposure

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted uterine dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv [a] (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007) [a]						
	All ages	430	n.a. [b]	0.21	729,608	0.06 (−0.14, 0.31)	0.33 (−0.79, 1.7)
	Age at exposure <20 y	n.a.	n.a.	0.22	n.a.	0.15 [c]	n.a.
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	22	~30 [d]	0.05	406,565	<0	<0
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	26	n.a.	0.025	n.a.	1.82 (<−1.93, 59.77)	n.a.
Mortality							
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	14	n.a.	0.0194	n.a.	−0.11 (<0, 131)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	8	n.a.	0.025	n.a.	<−1.93 (<−1.93, 45.49)	n.a.

TABLE 3.14 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	6	6 [e]	n.a.	12,247	0.6 (0.2, 1.8) [f]
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	3	n.a.	20.6 ml [g]	n.a.	0.7 (0.1, 3.8)

Notes
a Includes cases recorded as 'uterine cancers not otherwise specified'.
b Not available.
c Confidence interval not given.
d Based on cancer incidence rates for Stockholm.
e Based on national rates.
f Relative to an unexposed comparison group.
g Amount of Thorotrast administered.

In addition, the disease is more common in females of high parity and in those of low socioeconomic status. Long-term users of combined oral contraceptives are at higher risk, while those using barrier methods of contraception experience some protection. Cigarette smoking also increases the risk of the disease. While these additional risk factors may to some extent reflect variations in sexual behaviour, they also appear to have some independent effect of their own (Cancer Research UK, 2008).

3.14.2 Findings from studies of radiation exposure

3.14.2.1 Informative studies and evidence for association and causality.

Table 3.14 summarises the information available about cancer of the cervix. None of the studies provides significant evidence of an effect of radiation, although only the Life Span Study (LSS) includes a substantial number of cases (Preston et al, 2007). The limitations of the data collected in the Life Span Study have been described earlier in this report (see Chapter 2). Accordingly, while there is no evidence that the risk of cervical cancer is influenced by radiation, more information is needed before final conclusions can be drawn.

3.14.2.2 Gaps in knowledge

These include all aspects of radiation effects on cervical cancer. It would be particularly helpful to have a large body of data from a study other than the Life Span Study, but it is unlikely that this will be forthcoming.

3.15 Body of Uterus

3.15.1 General epidemiology

The great majority of cancers of the uterine body are adenocarcinomas derived from the endometrium, although sarcomas also occur and form a relatively high proportion of the uterine body cancers occurring in younger females. The incidence of uterine body cancer has been rising slowly in England and Wales since about 1993. Mortality, on the other hand, declined markedly between 1971 and 1995; since then, however, it has stabilised or has risen slightly, especially in the elderly. In the UK as a whole there were 7,045 new cases of uterine body cancer in 2006, while in the same year there were 1,741 deaths from the disease (Cancer Research UK, 2008).

While little is known about risk factors for uterine sarcomas, the reverse is true for endometrial cancer. A fundamental mechanism underlying the latter disease is the stimulatory effect of oestrogens on endometrial cell proliferation, insufficiently opposed by progestogens. Thus combined oral contraceptives have a favourable effect on risk, while unopposed oestrogens given as hormone replacement therapy are harmful. Obese females are at increased risk; this is probably due to the peripheral production of oestrogens in fatty tissue. Early menarche and late menopause tend to increase risk, probably reflecting the length of time that the uterus is exposed to natural oestrogens. Risk falls with increasing parity, possibly as a consequence of changes in the hormonal milieu during pregnancy. Diabetics are at increased risk, at least in part because they tend to be obese but perhaps also because of some specific effect of insulin and insulin-like growth factors (IGF). Cigarette smokers are at a slightly reduced risk of endometrial cancer, an effect only partially explained by the earlier occurrence of menopause in smokers (Cancer Research UK, 2008).

3.15.2 Findings from studies of radiation exposure

3.15.2.1 Informative studies and evidence for association and causality

Table 3.15 summarises the information available about uterine cancers (other than of the cervix). The Life Span Study is once again the source of most of the information; the most recent report includes 74 cases of cancer of the uterine body (Preston et al, 2007) in females with estimated doses below 0.005 Gy. While there was no statistically significant evidence of a radiation effect overall, there was a suggestion of such an effect in females exposed below the age of 20 years. However, the authors stress that this finding is based on very small numbers of excess cases and that it must be interpreted with caution. In the UK NRRW study (Muirhead et al 2009), the number of incident tumours in exposed workers (32) came close to representing a statistically significant excess. The same was not true for the mortality data but only 11 fatal cases were observed. There were no significant findings with regard to radiation effects in the 15-country study of nuclear workers by Cardis et al (2007) or in the study of Thorotrast-exposed patients by Travis et al (2003b).

Rather different results have been found in some studies in which females with benign uterine disease were treated with radiation (Dickson 1969; Wagoner, 1984; Inskip et al, 1990). In our view, however, these studies are hard to interpret because the underlying condition might well have been responsible for

TABLE 3.15 Risk estimates for incidence and mortality for uterine cancers (other than cervix) from studies of radiation exposure

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted uterine dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	All ages	74	n.a.[a]	0.21	729,608	0.29 (−0.14, 0.95)	0.30 (−0.16, 0.92)
	Age at exposure <20 y	n.a.	n.a.	0.22	n.a.	1.00 (0.14, 2.4)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	32	n.a.	0.025	n.a.	14.2 (1.06, 58.56)	n.a.
Mortality							
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	13	n.a.	0.0194	n.a.	0.16 (<0, 94.1)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	11	n.a.	0.025	n.a.	41.2 (<−1.93, 185)	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (uterine corpus) (Travis et al, 2003b)	5	4.5[b]	n.a.	12,247	0.6 (0.2, 1.8)[c]

Notes

a Not available.

b Based on national rates.

c Relative to an unexposed comparison group.

TABLE 3.16 Risk estimates for incidence and mortality for all uterine cancers combined from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted uterine dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	All ages	504	n.a. [a]	0.21	729,608	0.10 (−0.09, 0.33)	0.56 (<0, 0.33)
	Age at exposure <20 y	n.a.	n.a.	0.22	n.a.	0.37 (0.001, 0.86)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)	323	n.a.	0.17	1,061,690	0.17 (−0.10, 0.52)	0.44 (−0.27, 1.3)
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [b]	25	17.7 [c]	5.2	47,144 [d]	0.09 (−0.02, 0.19) [e]	0.29 (−0.06,0.78) [e,f]

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Mortality						
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	2	0.99 [c]	n.a.	n.a.	1.67 (95% CI 0.22, 9.63) [g]

Notes

a Not available.
b The values given exclude the period within 5 years of irradiation.
c Based on national mortality rates.
d Excluding the first 5 years following irradiation
e 95% CI here.
f Calculated as [(obs − exp) x 10^4 / (PY x mean dose)] with Poisson-based confidence interval.
g Relative to workers not monitored for any radionuclide.

the occurrence of the excess of cancer rather than the radiation exposure. The study of radiation treatment for cervical cancer by Boice et al (1988), which has also suggested that uterine body cancer risk might be increased by radiation, is similarly difficult to interpret. Accordingly, it must be concluded that there is no compelling evidence that radiation is a cause of uterine body cancer but that relevant information is largely absent.

3.15.2.2 Gaps in knowledge

These include all aspects of radiation effects. Studies are needed that include large numbers of cases exposed at different ages, a wide range of doses and without uncontrollable confounding effects such as those seen in studies of the treatment of benign gynaecological disease.

3.16 All Uterine Cancers

3.16.1 Findings from studies of radiation exposure

Relevant studies are summarised in Table 3.16. In view of the profound differences in aetiology and epidemiology between cancer of the cervix and cancer of the uterine body, it is difficult to draw conclusions from studies in which both sites of cancer are combined. In fact, none of the studies in Table 3.16 shows a significant effect of radiation on risk, a finding in keeping with the results of the studies dealing with cervical cancer and uterine body cancer separately.

3.17 Ovary

3.17.1 General epidemiology

The great majority of ovarian cancers are epithelial in origin, although germ cell tumours also occur, especially in the younger age groups. Incidence rates have been rising in England and Wales for at least the past three decades. This increase has occurred mostly in females over the age of 64 years; the relative stability of the rates in younger females may be related to high levels of use of combined oral contraceptives (see below). Overall mortality rates have remained fairly constant over the years, rises in mortality in females over the age of 64 years being compensated by declines in mortality among younger females. In England and Wales in 2002 there were 6,124 new cases of ovarian cancer, while in 2008 there were 4,373 deaths from the disease (ONS, 2009).

A number of risk factors are known for ovarian cancer but the aetiology of the disease remains obscure. As already indicated, combined oral contraceptives provide an important degree of protection against the disease, which is dependent on the duration of use. The reduction in risk after several years of use may be as great as 50%, and this effect persists long after discontinuation of use. On the other hand, hormone replacement therapy slightly increases risk. Increasing parity is strongly associated with a decreasing risk. Some studies have suggested that perineal application of talcum powder has a modest adverse effect, while females who have undergone tubal surgery for contraceptive reasons are somewhat less likely to develop ovarian cancer than other females. Family history is an important risk factor for ovarian cancer,

TABLE 3.17 Risk estimates for ovarian cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted ovarian dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	103	n.a. [a]	0.21	729,608	0.61 (0.00, 1.5)	0.56 (0.02, 1.3)
2.2.3	Cervical cancer case–control (Boice et al, 1988)	299	664 [b]	32.1	n.a.	0.01 (−0.02, 0.14) [c]	0.05 (−0.08, 0.60) [d]
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	15	~15 [e]	0.05	n.a.	0.62 [f]	0.33
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	15	n.a.	0.025	n.a.	<−1.93 (<−1.93, 61.13)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)	85	n.a.	0.17	1,061,690	0.94 (0.07, 2.0)	0.63 (0.23, 1.2)
3.2.1	Benign gynaecological disease – USA (Inskip et al, 1990) [g]	37	23.7	2.3	71,958	0.41 (−0.69, 1.51) [h]	n.a.
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [i]	18	15.6 [j]	5.3	47,144	0.02 (−0.08, 0.12) [k]	0.1 (−0.19, 0.51) [k,l]
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	35	n.a.	0.0194	n.a.	<0	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	18	n.a.	0.025	n.a.	<−1.93 (<−1.93, 89.13)	n.a.

TABLE 3.17 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	9	2.1 [m]	n.a.	12,247	4.3 (1.1, 24.3) [n]
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	3	n.a.	20.6 ml [o]	n.a.	0.8 (0.1, 4.4)
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	2	1.1 i	n.a.	n.a.	4.88 (0.49, 48.44) [p]

Notes

a Not available.
b Calculated as the ratio of the observed cases to the estimated relative risk.
c Estimated based on 10-year survivors.
d Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
e Based on cancer incidence rates for Stockholm.
f Not statistically significantly different from zero.
g The observed and expected numbers of cases are for 10-year survivors.
h Wald-type confidence interval.
i The values given exclude the period within 5 years of irradiation.
j Based on national mortality rates.
k 95% CI here.
l Calculated as [(obs – exp) x 10^4 / (PY x mean dose)] with Poisson-based confidence interval.
m Based on national incidence rates.
n Relative to an unexposed comparison group.
o Amount of Thorotrast administered.
p Relative to workers not monitored for any radionuclide.

a woman with an affected first-degree relative experiencing up to a three-fold increase in risk. The BRCA1 and BRCA2 gene mutations are important in this respect, but high risk genes are thought to be responsible for only about 30% of the excess familial ovarian cancer risk (Cancer Research UK, 2008).

3.17.2 Findings from studies of radiation exposure

3.17.2.1 Informative studies and evidence for association and causality

The relevant studies are summarised in Table 3.17. The Life Span Study incidence data for ovarian cancer indicate a borderline significant association between exposure to radiation and ovarian cancer (Preston et al, 2007). For all exposure ages, risks in the highest dose category were increased relative to those in the lowest dose category. Mortality data from the Life Span Study also showed a significant positive association between radiation exposure and ovarian cancer risk (Preston et al 2003). The incidence data and the mortality data, however, obviously cannot be regarded as independent.

The study by Boice et al (1988) of females treated with high dose radiation for cervical cancer is hard to interpret, but an overall reduction in the risk of ovarian cancer (which was of borderline significance) was found. Nonetheless, there was some suggestion of a positive dose–response relationship among the 10-year survivors.

The remaining studies shown in Table 3.17 all include small numbers of cases. No significant effect of radiation was found in the studies by Lundell and Holm (1995), Darby et al (1994) or Muirhead et al (2009). On the other hand, the study of radioactive Thorotrast by Travis et al (2003b) did find an excess of ovarian cancers in the treated group which was just statistically significant. Inskip et al (1990), in their study of cancer mortality following radium treatment for uterine bleeding, divided their cases of gynaecological cancer into uterine cancers and cancers of other genital organs. They noted that the majority of the latter group were ovarian cancers. A positive dose–response relationship was found over the range 0 to 4 Gy, which approached statistical significance.

While falling short of certainty, it is concluded that exposure to radiation may increase the risk of ovarian cancer and that the risk increases with increasing dose.

3.17.2.2 Estimates of radiation risks

The only study providing any useful estimate of risk is the Life Span Study. The relevant data are given in Table 3.25.

3.17.2.3 Modifying factors

No reliable information is available about modifying factors, although the Life Span Study suggests that age at exposure does not influence the risk.

3.17.2.4 Gaps in knowledge

These include all aspects of radiation effects. Unfortunately, it appears unlikely that studies of sufficient size will ever be done to enable dose effects, type of exposure and modifying factors to be properly assessed.

3.18 Prostate

3.18.1 General epidemiology

Prostate cancer is the most common cancer in males in the UK (over 30,000 cases in 2005) and many other Western countries. In contrast, the disease is much rarer in developing and Asian countries (less than 2 per 100,000 males in China). The highest rates are found in black Americans (www-dep.iarc.fr/). Incidence rises very steeply with age. Prostate cancer incidence in the UK has increased rapidly in recent years, from 33 per 100,000 men in 1975 to 98 per 100,000 in 2004 (Cancer Research UK, 2008). In contrast, mortality peaked at 30 per 100,000 men in the mid-1990s and has subsequently declined to approximately 25 per 100,000. Much of the recent increase in prostate cancer has been attributed to the increase in prostate-specific antigen (PSA) screening, which can detect asymptomatic disease.

The causes of prostate cancer are poorly understood. Growth of the prostate is dependent on testosterone, and prostate cancer is responsive to anti-androgen therapy, suggesting that hormonal exposure is important. Apart from the variation in risk by ethnic group there are no definite risk factors, although geographical variation in incidence suggests that dietary factors are important.

3.18.2 Findings from studies of radiation exposure

3.18.2.1 Informative studies and evidence for association and causality

Table 3.18 summarises findings from cohort and case–control studies of prostate cancer among radiation-exposed groups, specifically for studies in which individual assessments of exposures have been made. The most informative study for external exposure is the Life Span Study, in which 156 cases and 53 deaths from prostate cancer have been identified in the most recent analyses (Preston et al, 2003, 2007). The observed number of cases was only slightly, and not significantly, greater than that expected on the basis of background incidence rates, and there was no evidence of a trend in relative risk with increasing dose. Among studies of patients medically exposed to significant doses, there is evidence of an excess risk in the cohort of ankylosing spondylitis patients (Weiss et al, 1994), but no evidence of an excess risk in the cohort of peptic ulcer patients (Carr et al, 2002).

No significant excess incidence or mortality has been observed in studies of radiation workers.

The ERR from the Life Span Study, namely 0.11 Sv^{-1} (90% CI −0.1, 0.54), is similar to that from the ankylosing spondylitis study. These results suggest that external low LET radiation exposure may be associated with an increased risk of prostate cancer, but the ERR is much lower than for other common solid tumours. Preston et al (2007) estimate that 2.2% of prostate cancers in the Life Span Study are attributable to radiation exposure, compared to 10.7% for all solid tumours.

Evidence on the effect of internal low LET exposure is very limited. One case–control study of United Kingdom Atomic Energy Authority workers reported a significant association with exposure, based on 28 cases (Rooney et al, 1993). Continued follow-up of these workers found a significantly lower mortality from prostate cancer in later years in many of the subsets that were previously identified as high risk (Atkinson et al, 2007).

TABLE 3.18 Risk estimates for prostate cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted bladder dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	156	n.a. [a]	0.21	436,180	0.11 (−0.10, 0.54)	0.34 (−0.64, 1.6)
6.4	Canadian National Dose Registry (Sont et al, 2001)	232	279	0.0066 (whole cohort) 0.011 (males)	n.a.	0.1 (<0, 3.5)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	1,516	n.a.	0.025	n.a.	−1.80 (−0.65, 0.43)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)	53	n.a.	0.19	666,870	0.21 (<−0.3, 0.96)	0.18 (<−0.2, 0.75)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [b]	88	64.7 [c]	2.18	n.a.	0.14 (0.02, 0.28) [d,e]	n.a.
3.3.2	Peptic ulcer (Carr et al, 2002)	30	24.2 [c]	0.1	41,779 [f]	<0 [g] (<0, 4.5) [e]	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	301	n.a.	0.0194	n.a.	0.77 (<0, 4.58)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	302	n.a.	0.025	n.a.	0.42 (−0.31, 1.41)	n.a.

TABLE 3.18 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
10.1	UK Atomic Energy Authority workers: case–control study (Rooney et al, 1993)	28 [h]	n.a.	n.a.	n.a.	2.36 (1.26, 4.43)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
11.1	Radium-224 TB and ankylosing spondylitis (Nekolla et al, 1999)	16	~12	n.a.	n.a.	~1.3
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	14	3.1 [i]	n.a.	13,233	4.5 (1.6, 16.3) [j]
Mortality						
12.1	German Thorotrast patients (van Kaick et al, 1999; Becker et al, 2008)	18	n.a.	20.6 ml [k]	n.a.	2.1 (1.0, 4.3) [j]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	32	31.7 [c]	n.a.	n.a.	0.90 (0.56, 1.43) [l]

Notes

a Not available.
b The values given exclude the period within 5 years of first treatment.
c Based on national mortality rates.
d Dose–response analysis based on the number of treatment courses given.
e 95% CI here.
f Value for all patients who received radiotherapy.
g Based on patients with more than 10 years of follow-up and dividing the overall ERR by the average dose.
h Men who worked in environments potentially contaminated with tritium, chromium-51, iron-59, cobalt-60 or zinc-65.
i Based on national incidence rates.
j Relative to an unexposed comparison group.
k Amount of Thorotrast administered.
l Relative to workers not monitored for any radionuclide.

With regard to internal high LET exposure, one cancer incidence analysis of the international Thorotrast cohort of Danish and Swedish patients found a significant association with exposure, based on 14 cases (Travis et al, 2003b). A mortality study of German Thorotrast patients (Becker et al, 2008) also showed an excess, although the statistical significance of the result was marginal. Other studies have shown no effect. There was some evidence of excess prostate cancer in the study of Carpenter et al (1988), but only among workers monitored for radionuclides other than plutonium or tritium.

3.18.2.2 Estimates of radiation risks

The ERR of prostate cancer in the latest Life Span Study incidence data (Preston et al, 2007) is 0.11 Sv^{-1} (90% CI −0.1, 0.54); the corresponding EAR is 0.34 10^{-4} PY^{-1} Sv^{-1} (90% CI −0.64, 1.6). The ERR estimate from the ankylosing spondylitis study (0.14 Sv^{-1}) is similar. In the latest Life Span Study mortality data (Preston et al, 2003), the ERR was 0.21 (90% CI −0.3, 0.96).

3.18.2.3 Modifying factors

There is no clear evidence from the Life Span Study that the relative risk is modified by age at exposure or attained age (Preston et al, 2007). However, the number of cases to date among males exposed below the age of 10 years is small, so this analysis lacks power.

3.18.2.4 Gaps in knowledge

There remains no definite evidence as to whether radiation exposure is associated with a risk of prostate cancer. Further follow-up of cohorts, particularly the Life Span Study, may clarify this. There is little information on the risks associated with internal high or low LET radiation.

3.19 Testis

3.19.1 General epidemiology

Testicular cancer is a relatively rare cancer with about 2,000 cases diagnosed in 2005 in the UK. The disease is rare in non-Caucasians and in elderly men, with over half of the cases being diagnosed in 15–35 year olds. Testicular cancer incidence in the UK has increased in recent years, from 3.3 per 100,000 men in 1975 to 7.0 per 100,000 in 2005 and most of this increase has occurred in men younger than 45 years of age (Cancer Research UK, 2008). In contrast, mortality rates have decreased since the introduction of platinum-based chemotherapy in the 1970s, from about 1 per 100,000 men in 1975 to 0.2 per 100,000 in 2005.

The risk factors for testicular cancer include undescended testicles, family history of testicular cancer, HIV infection and Klinefelter's syndrome.

About 95% of testicular cancers are germ-cell tumours and 40% of these are seminomas. Most of the remaining 5% are lymphomas.

TABLE 3.19 Risk estimates for testicular cancer incidence and mortality from studies of radiation exposure

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
3.1.8	Stockholm skin haemangioma (Lundell and Holm, 1995)	7	~8	0.05	n.a. [a]	1.6 [b]	0.76
6.4	Canadian National Dose Registry (Sont et al, 2001)	75	73.7	0.0066 (whole cohort) 0.011 (males)	n.a.	38.3 1.4, 147.9)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	116	n.a.	0.025	n.a.	1.02 <–1.93, 7.21)	n.a.
Mortality							
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	27	n.a.	0.0194	n.a.	<0	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	13	n.a.	0.025	n.a.	3.29 <–1.95, 42.71)	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Mortality						
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	4	2.6 [c]	n.a.	n.a.	2.36 (0.55, 8.91) [d]

Notes

a Not available.
b Not statistically significantly different from zero.
c Based on national mortality rates.
d Relative to workers not monitored for any radionuclide.

3.19.2 Findings from studies of radiation exposure

Table 3.19 summarises the information available about testicular cancer. Because it is a relatively rare cancer the number of cases in most of the studies is small (below 30) and the results from these studies have been inconsistent. The Canadian National Dose Registry and the UK NRRW are the only studies with reasonable numbers of cases (75 and 116, respectively) and in both these studies there was evidence of an increased risk, although the confidence intervals were wide and non-significant in the UK NRRW. In the workers monitored for internal exposure to plutonium there was also evidence of a significantly increased risk of testicular cancer mortality (based on 4 cases). However, in two occupational studies there was no evidence of an association. The limitations of the data collected in the nuclear worker studies have been described previously (see Chapter 2). It is currently unclear whether radiation causes testicular cancer – more information is needed before final conclusions can be drawn.

3.19.2.1 Gaps in knowledge

These include all aspects of radiation effects on testicular cancer. It would be particularly helpful to have a body of data from studies other than nuclear worker studies, but given the relative rarity of this cancer it is unlikely that this will be forthcoming.

3.20 Bladder

3.20.1 General epidemiology

Bladder cancer accounts for less than 5% of total cancer incidence and less than 2% of total cancer mortality in industrialised countries. There is wide international variation in bladder cancer incidence, with high rates in Europe and North America and low rates in Latin America and Asia. Incidence increases steeply with age and is substantially more common among males than females – in some countries the ratio can reach 5 : 1 (Hankey et al, 1993; Parkin et al, 2002). Incidence increased from the 1960s to the 1980s, but recently has begun to stabilise. Mortality rates have been decreasing for both males and females and for all ages. The temporal trends are influenced by changes in detection and improvements in survival. In the UK, incidence rates in 2004 were 19.5 and 4.7 cases per 100,000 persons for males and females, respectively, and in 2005 mortality rates of 8.1 and 2.8 deaths per 100,000 persons for males and females, respectively, were recorded (Cancer Research UK, 2008).

Cigarette smoking is a leading cause of bladder cancer. In Western countries, approximately 50% of the cases of cancer in males and 30% in females have been attributed to smoking. Occupational exposures to carcinogens, particularly to aromatic amines, and urinary tract infections especially among females also are associated with an increased risk of bladder cancer. Use of phenacetin-containing analgesics and cyclophosphamide, as well as exposure to arsenic in drinking water and *S. haematobium* infection, are also suspected risk factors for bladder cancer (Hankey et al, 1993; McCredie, 1994; Silverman et al, 1996).

TABLE 3.20 Risk estimates for bladder cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with doses of 0.005 Sv or more (weighted bladder dose for the incidence data or weighted urinary tract dose for the mortality data). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	132	n.a. [a]	0.22	436,180	0.61 (0.11, 1.2) [b]	3.8 (0.2, 8.0) [b]
	Females	90	n.a.	0.20	729,608	1.9 (0.79, 3.4) [b]	2.6 (1.1, 4.4) [b]
	Both sexes						
	Age at exposure < 20 y	48	n.a.	0.21	586,255	1.32 (0.28, 4.1) [c]	4.8 (0.7, 16) [c]
	20–39 y	80	n.a.	0.21	378,204	1.23 (0.59, 2.1) [b]	3.2 (1.1, 5.4) [b]
	40+ y	94	n.a.	0.19	201,330	1.15 (0.34, 2.5) [d]	2.1 (0.5, 4.5) [d]
	All	222	n.a.	0.21	1,165,788	1.23 (0.59, 2.1) [b]	3.2 (1.1, 5.4) [b]
2.2.3	Cervical cancer case–control (Boice et al, 1988)	267	65.9 [e]	30–60	n.a.	0.07 (0.02, 0.17) [f]	0.12 (0.04, 0.30) [g]
6.4	Canadian National Dose Registry (Sont et al, 2001) [h]	139	183	0.0066 (whole cohort) 0.011 (males)	n.a.	1.4 (<0, 8.2)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	748	n.a.	0.025	2,388,848	0.65 (−0.15, 1.72)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	56	n.a.	0.19	666,870	1.1 (0.2, 0.5)	0.7 (0.1, 0.14)
	Females	43	n.a.	0.18	1,061,690	1.2 (0.10, 3.1)	0.33 (0.02, 0.74)

TABLE 3.20 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
3.2.1	Benign gynaecological disease – USA (Inskip et al, 1990) [i]	19	9.0	6.00	71,958	0.20 (0.08, 0.35)	0.23 (0.08, 0.44) [j]
3.2.2	Metropathia haemorrhagica – UK (Darby et al, 1994) [k]	20	6.7 [l]	5.20	47,144	0.40 (0.15, 0.66) [m]	n.a.
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [n]	71	46.1	2.18	287,095	0.24 (0.09, 0.41) [m,o]	0.40 (0.15, 0.69) [m]
3.3.2	Peptic ulcer (Carr et al, 2002)	13	8.84 k	0.2	41,779	2.4 (−0.9, 7.3) [p,q]	5.0 (−1.9, 15) [n,q]
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	145	n.a.	0.0194	5,192,710	<0	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	301	n.a.	0.025	2,433.573	0.4 (−0.64, 2.07)	n.a.

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	8	6.7 [r]	n.a.	25,480	0.8 (0.3, 1.9) [s]
14.2.1	Drilled well users (Kurttio et al, 2006)	61	n.a.	*Median activity concentration* Radon: 130 Bq l^{-1} Radium: 0.01 Bq l^{-1} Uranium: 0.06 Bq l^{-1}		*RR per log(100 Bq l^{-1})* Radon: 1.02 (0.68, 1.54) Radium: 0.73 (0.21, 2.50) Uranium: 0.77 (0.32, 1.89)
Mortality						
12.1	German Thorotrast cohort (Becker et al, 2005)	5	5.2	n.a.	n.a.	2.7 (0.5, 17.3)
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	15	23.1 [l]	n.a.	n.a.	0.72 (0.37, 1.34) [t]

TABLE 3.20 ***continued***

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e Calculated as the ratio of the observed cases to the estimated relative risk.
f Estimated based on 10-year survivors.
g Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
h Values for males only; the publication did not cite a risk factor for the full population of males and females.
i The observed, expected numbers and person-years of follow-up of cases are for 10-year survivors.
j Calculated as $[(obs - exp) \times 10^4 / (PY \times mean\ dose)]$ with Poisson-based confidence interval.
k The values given exclude the period within 5 years of irradiation.
l Based on national mortality rates.
m 95% CI here.
n The values given exclude the period within 5 years of first treatment.
o Dose–response analysis based on the number of treatment courses given.
p Based on patients with more than 10 years of follow-up and dividing the overall ERR by the average dose.
q Values from UNSCEAR (2008).
r Based on national incidence rates.
s Relative to an unexposed comparison group. Amongst exposed patients, there was no statistically significantly trend in risk with a measure of cumulative exposure.
t Relative to workers not monitored for any radionuclide.

3.20.2 Findings from studies of radiation exposure

3.20.2.1 Informative studies and evidence for association and causality

Based on the data presented in Table 3.20, there is evidence of an association with radiation exposure. A summary of results from studies in relation to external low LET exposure is shown in Table 3.20. There is convincing evidence of a relation between low LET radiation exposure and bladder cancer risk based on the Life Span Study incidence and mortality data (Preston et al, 2003, 2007), as well as on studies of several populations medically exposed to radiation for benign diseases (Inskip et al, 1990; Darby et al, 1994; Weiss et al, 1994; Carr et al, 2002) and populations receiving radiotherapy for malignant diseases (Boice et al, 1988; Neugut et al, 1997; Travis et al, 1996, 1997; Brenner et al, 2000). The most recent Life Span Study mortality report observed little difference in the ERR between the sexes (1.1 and 1.2), although the estimated EAR for males was about twice that for females (0.7 and 0.33, respectively) (Preston et al, 2003). No information on time patterns was provided in this report. The risk estimates from the studies of the Life Span Study cohort are generally greater than those from most other studies, as can be seen from Table 3.20. However, this difference may be related to the phenomenon of cell killing arising from the very high doses involved in many of the medical studies.

In a study of cancer following radiotherapy for peptic ulcer (Carr et al, 2002), based on a small number of deaths due to bladder cancer among irradiated and non-irradiated patients (13 and 8, respectively), the relative risk for radiotherapy was estimated to be 1.49 (95% CI 0.50, 4.4) in the period 11–62 years after treatment. With a mean bladder dose of 0.2 Gy, an ERR of 2.5 (90% CI <0, 17.2) could be estimated.

Although individual organ doses frequently are not available, several, but not all, studies of second cancers have reported an association between bladder cancer risk and high therapeutic radiation doses (eg Boice et al, 1988; Kaldor et al, 1995; Travis et al, 1995, 1996, 1997; Neugut et al, 1997; Pawlish et al, 1997; Brenner et al, 2000; Pickles and Phillips, 2002; Chrouser et al, 2005).

No clear excess of bladder cancer incidence or mortality has been shown in a number of studies of nuclear workers, including those of the Canadian National Dose Registry (Sont et al, 2001), the UK NRRW (Muirhead et al, 1999, 2009), the combined 15-country analysis of nuclear workers (Cardis et al, 2007) and several smaller studies (Frome et al, 1990; Wiggs et al, 1994; McGeoghegan and Binks, 2000a,b, 2001; Iwasaki et al, 2003; McGeoghegan et al, 2003; Atkinson et al, 2004). An elevated risk of bladder cancer has been reported among Chinese radiology workers, particularly those who worked before 1970 (Wang et al, 2002). In contrast, neither bladder cancer incidence nor mortality was increased in a cohort of US radiological technologists (Mohan et al, 2003; Sigurdson et al, 2003).

Information on bladder cancer risks from internal low LET radiation exposure is limited, and there is little evidence of a link between bladder cancer and exposure to iodine-131 (Hall et al, 1991, 1992; Holm et al, 1991; de Vathaire et al, 1997; Ron et al, 1998) with the exception of two relatively small studies of thyroid cancer (Edmonds and Smith, 1986) and of hyperthyroid patients (Franklyn et al, 1999) treated with iodine-131. High doses of iodine-131 are often used to treat thyroid cancer. In another study of internal low LET radiation exposure, bladder cancer incidence was elevated, but the lower confidence interval included unity (standardised incident ratio, SIR, for iodine-131 therapy compared to no iodine-131 therapy = 1.6; 95% CI 0.6, 4.5) following iodine-131 exposure during treatment for thyroid cancer (Rubino et al, 2003). This study is the largest conducted to date and included cohorts of patients from France, Sweden and Italy. The bladder is one of the few organs that concentrate iodine (UNSCEAR, 2000); the iodine-131 dose to the bladder from this treatment is about 2 Gy.

The risk of bladder cancer associated with exposure to internal high LET radiation is unclear. In general, no risk was seen among patients exposed to Thorotrast as a contrast medium (Andersson et al, 1995; dos Santos Silva et al, 1999; Mori et al, 1999a; Nekolla et al, 1999; van Kaick et al, 1999; Wick et al, 1999; Travis et al, 2003b). In a Finnish study of persons exposed to dissolved radioactive material (predominantly from radon-222, but also from uranium-234 and -238, radium-226, polonium-210 and lead-210), an elevated incidence of urinary bladder cancer was not statistically significantly associated with ingested aggregate quantities of radon, radium or uranium, nor with the aggregate bladder dose (Kurttio et al, 2006).

3.20.2.2 Estimates of radiation risks

As given in Table 3.20, the ERR of bladder cancer in the latest Life Span Study incidence data (Preston et al, 2007) for exposure at age 30 is 1.23 Sv^{-1} (90% CI 0.59, 2.1); the corresponding EAR is 3.2 10^{-4} PY^{-1} Sv^{-1} (90% CI 1.1, 5.4). In the latest Life Span Study mortality data the ERR for males given by Preston et al (2003) is 1.1 Sv^{-1} (90% CI 0.2, 2.5) and for females is 1.2 Sv^{-1} (90% CI 0.10, 3.1); the corresponding EAR for males is 0.7 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.1, 1.4) and for females is 0.33 10^{-4} PY^{-1} Sv^{-1} (90% CI 0.02, 0.74).

3.20.2.3 Modifying factors

In the Life Span Study, the effects of age and sex on the risks are unclear. A statistically significant difference between the risks for the two sexes, with the ERR for females exceeding that for males by a factor of about five, was seen in the older incidence data, although no significant difference was observed when an EAR model was used (Thompson et al, 1994). Based on the older mortality data, the point estimates of the ERRs and EARs for males are higher than those for females, although the differences are not statistically significant (Pierce et al, 1996). Neither the older mortality data (Pierce et al, 1996) nor the older incidence data (Thompson et al, 1994) exhibited statistically significant variation with age at exposure for either the ERR or the EAR. There are no statistically significant variations in bladder cancer relative risk by age at exposure, time since exposure or attained age in the latest Life Span Study incidence data (Preston et al, 2007). The EAR increases with attained age in the same dataset.

3.20.2.4 Gaps in knowledge

There is limited information on risks from internal high and low LET radiation exposure. Potential interactions between smoking and radiation exposure are not known and need to be studied.

3.21 Kidney

3.21.1 General epidemiology

The estimated annual number of cases of kidney cancer worldwide is approximately 189,000 and the associated annual number of deaths is about 91,000 (Ferlay et al, 2001). The incidence of renal cell carcinoma is about eight-fold higher in developed countries than developing ones, with a range of annual age-standardised incidence of 0.5 per 100,000 persons in parts of India to 20.0 and 10.2 per 100,000 males and females, respectively, in parts of Czech Republic (Parkin et al, 2002). These differences are party due to the relative availability of ultrasound, CT and MRI scans (Godley and Kim, 2002). In the UK, incidence rates in 2004 were 12.8 and 6.5 cases per 100,000 persons for males and females, respectively, and in 2005 mortality rates of 6.1 and 2.9 deaths per 100,000 persons for males and females, respectively, were recorded (Cancer Research UK, 2008).

Well-documented risk factors for the disease include cigarette smoking, obesity, hypertension and acquired polycystic kidney disease. Risk factors for which there is some evidence, but for which links are as yet unproven, are renal transplantation, HIV infection, heavy metals exposure (especially to cadmium and lead), exposure to chlorinated solvents, asbestos and phenacitin analgesics, and urinary tract infections. Other factors, such as higher levels of physical activity, of vegetable consumption, and of calcium and vitamin E supplements, may be protective (Godley and Kim, 2002; Murai and Owa, 2004). There is a clear familial component to the disease: the relative risk for a sibling, but not for parents, of an affected person is about 2.5, thereby suggesting recessive genetic risk (Hemminki and Li, 2004). A study in Iceland reported that nearly 60% of kidney cancer patients also had a first- or second-degree family member with kidney cancer (Gudbjartsson et al, 2002). At the molecular level, common findings in familial and sporadic renal cell carcinoma are a loss of the terminal portion of the small arm of chromosome 3, sometimes with a translocation near the breakpoint 3p13 in familial cases, and/or a somatic mutation or hypermethylation in the 3p segment on or near the von Hippel-Lindau (VHL) gene locus (Godley and Kim, 2002).

3.21.2 Findings from studies of radiation exposure

3.21.2.1 Informative studies and evidence for association and causality

Based on the data presented in Table 3.21, the evidence of an association with radiation exposure is unclear. A summary of results from studies in relation to external low LET exposure is shown in Table 3.21. The data are quite sparse for radiation exposure and kidney cancer risk. In the Life Span Study cohort, the association between radiation dose and kidney cancer incidence based on follow-up to the end of 1998 was not statistically significant, and a bit lower than that seen for many other sites (ERR Sv^{-1} = 0.13) (Preston et al, 2007). Similarly, in the Life Span Study mortality data, the dose–response association was not statistically significant for either males or females, although the risk was nominally larger for females (ERR Sv^{-1} = 0.97; 90% CI <–0.3, 3.8) than for males (ERR Sv^{-1} = –0.02; 90% CI <–0.3, 1.1) (Preston et al, 2003).

Studies of several cohorts of cervical cancer patients receiving radiotherapy did not indicate significant elevations in risk (compared with general population rates or unirradiated comparison groups) (Boice et al, 1985; Storm et al, 1992; Kleinerman et al, 1995). However, a case–control study nested within the largest cervical cancer cohort study showed a positive dose–response relationship (ERR Sv^{-1} = 0.71; 95% CI 0.03, 2.2) (Boice et al, 1988). The UK ankylosing spondylitis study also showed an elevation in kidney cancer risk in association with generally high (radiotherapeutic) doses (ERR Sv^{-1} = 0.10; 95% CI 0.02, 0.20) (Weiss et al, 1994). Two smaller studies of radiotherapy for uterine bleeding or peptic ulcer did not exhibit raised risks (Inskip et al, 1990; Carr et al, 2002) but they had low statistical power.

A number of studies of radiation workers have shown no positive dose–response association or clear excess of kidney cancers. For example, in the UK NRRW (Muirhead et al, 2009), 170 deaths due to kidney cancer were observed compared with 190.2 expected from national rates and there was a negative trend in mortality with external film badge dose: the ERR Sv^{-1} was <–1.03 (90% CI <–1.52, 0.08). There was a positive trend, albeit not statistically significant, with increasing external dose in the IARC 15-country study, based on 127 deaths from kidney cancer: the ERR Sv^{-1} was 2.26 (90% CI <0, 14.9) (Cardis et al, 2007).

The study of the Canadian National Dose Registry (Sont et al, 2001) reported 69 kidney cancer deaths versus 91.1 expected (SMR = 0.76; 90% CI 0.61, 0.93) among male workers, and 21 kidney cancer deaths versus 26.5 expected (SMR = 0.79; 90% CI 0.53, 1.14) among female workers. Generally non-significant negative trends of kidney cancer mortality with external dose were observed in a UK cohort of workers at a uranium production facility: only with a 20-year lag was the trend with dose (non-significantly) positive (McGeoghegan and Binks, 2000a). Similarly, generally negative trends of kidney cancer mortality rates with external film badge dose were observed among workers at the Chapelcross plant (McGeoghegan and Binks, 2001). The study of Artalejo et al (1997) reported a slight excess of kidney cancer mortality among workers for the Spanish Nuclear Energy Board; the SMR was 1.26 (95% CI 0.34, 3.21), based on just 4 cancer deaths, of which 2 were among the 27% of the cohort who had been miners and may have been exposed to alpha radiation (Artalejo et al, 1997). The statistical power of all the occupational studies is limited by the low levels of dose.

Three studies have examined kidney cancer risk in relation to internal exposure to low LET radiation emitters. A Swedish study of cancer incidence following iodine-131 treatment for hyperthyroidism reported

significantly more kidney cancers in the iodine-131-treated group than expected based on general population rates. However, a dose–response analysis was not reported, so it is unknown whether the excess was associated primarily with hyperthyroidism or with radiation exposure (Holm et al, 1991). A US study of mortality following hyperthyroidism treatment showed no excess risk for kidney cancer (Ron et al, 1998). A study of 6,841 Swedish, French and Italian patients treated with a mixture of conventional (external beam) radiotherapy and iodine-131 for thyroid cancer recorded a modest, and statistically significant, increase in kidney cancer incidence (SIR = 2.6; 95% CI 1.7, 3.8; 31 cases) (Rubino et al, 2003). However, there was no relation with iodine-131 exposure; risks were comparable in the group treated with and without iodine-131 (SIR = 2.6 in both cases) (Rubino et al, 2003).

The only recent study of kidney cancer risk in relation to internal high LET radiation exposure was of a group of Danish, Swedish and US patients who received the diagnostic contrast medium Thorotrast, and a companion group who received a non-radioactive contrast medium (Travis et al, 2003b). There were 12 cases of kidney cancer in the exposed group, and 4 in the control group, representing a relative risk of 5.7 (95% CI 1.9, 21.0; $p < 0.05$) (Travis et al, 2003b). The relative risk also increased with increasing interval of follow-up ($p<0.001$), suggesting a causal association between Thorotrast exposure and the risk of kidney cancer; however, there was no statistically significant trend with increasing volume of injected Thorotrast ($p = 0.23$). No statistically significant excess of kidney cancer has been observed in German or Japanese Thorotrast-exposed groups (Mori et al, 1999b; van Kaick et al, 1999). Ishikawa et al (1993) have estimated that the kidney in Thorotrast patients would typically receive a relatively modest radiation dose, of about 1.5 mGy per year. Given that the kidney appears to be relatively radio-resistant, it is unlikely that the excess risk observed in the three-country study is causally associated with the Thorotrast exposure.

In a Finnish study of persons exposed to dissolved radioactive material (predominantly from radon-222, but also from uranium-234 and -238, radium-226, polonium-210 and lead-210), the incidence of kidney cancer was not statistically significantly associated with ingested aggregate quantities of radon, radium or uranium, nor with the aggregate kidney dose (Kurttio et al, 2006).

3.21.2.2 Estimates of radiation risks

As given in Table 3.21, the ERR of renal cell cancer in the latest Life Span Study incidence data (Preston et al, 2007) is 0.13 Sv^{-1} (90% CI −0.25, 0.75); the corresponding EAR is 0.08 10^{-4} PY^{-1} Sv^{-1} (90% CI −0.16, 0.44). In the latest Life Span Study mortality data (Preston et al, 2003), the ERR for kidney cancer for males is −0.02 Sv^{-1} (90% CI <−0.3, 1.1) and for females is 0.97 Sv^{-1} (90% CI <−0.3, 3.8); the corresponding EAR for males is −0.01 10^{-4} PY^{-1} Sv^{-1} (90% CI −0.1, 0.28) and for females is 0.14 10^{-4} PY^{-1} Sv^{-1} (90% CI <−0.1, 0.42).

3.21.2.3 Modifying factors

In the Life Span Study and in other groups, the effects of age and sex on the risks are unclear. Based on small numbers of cases and deaths, it appears that the ERR may be greater for females than for males, both in the Life Span Study incidence data (Preston et al, 2007) and in the corresponding mortality data (Preston et al, 2003) (Table 3.21).

3.21.2.4 Gaps in knowledge

There is very limited information on risks for this endpoint, and in particular modifying factors such as age and sex. There is also limited information on risks from internal high and low LET radiation exposure.

TABLE 3.21 Risk estimates for kidney cancer incidence and mortality from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with doses of 0.005 Sv or more (weighted bladder dose for the incidence data or weighted urinary tract dose for the mortality data). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	70	n.a. [a]	0.21	1,165,787	0.13 (−0.25, 0.75)	0.08 (−0.16, 0.44)
2.2.3	Cervical cancer case–control (Boice et al, 1988)	134	109 [b]	2.0	n.a.	0.71 (−0.03, 2.24) [c]	1.10 (0.05, 3.50) [d]
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	296	n.a.	0.025	2,388,848	−0.41 (−1.22, 1.09)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	18	n.a.	0.23	666,870	−0.02 (<−0.3, 1.1)	−0.01 (−0.1, 0.28)
	Females	21	n.a.	0.23	1,061,690	0.97 (<−0.3, 3.8)	0.14 (<−0.1, 0.42)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [e]	35	21.6 [f]	6.08	287,095	0.10 (0.02, 0.20) [g,h]	0.08 (0.02, 0.15) [g,i]
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	127	n.a.	0.0194	5,192,710	2.26 (<0, 14.9)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 1999)	187	n.a.	0.025	2,433.573	−1.03 (−1.52, 0.08)	n.a.

TABLE 3.21 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Incidence						
12.2	International Thorotrast cohort – Danish and Swedish patients (Travis et al, 2003b)	12	2.1 [j]	n.a.	25,480	5.7 (1.9, 21.0) [k]
14.2.1	Drilled well users (Kurttio et al, 2006)	51	n.a.	*Median activity concentration* Radon: 130 Bq l^{-1} Radium: 0.01 Bq l^{-1} Uranium: 0.06 Bq l^{-1}		*RR per log (100 Bq l^{-1})* Radon: 0.81 (0.47, 1.37) Radium: 0.12 (0.01, 1.10) Uranium: 0.92 (0.36, 2.35)
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	5 (male)	n.a.	20.6 ml [l]	n.a.	0.9 (0.2, 3.0)
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	12	12.0 [f]	n.a.	n.a.	0.89 (0.41, 1.87) [m]

Notes

a Not available.
b Calculated as the ratio of the observed cases to the estimated relative risk.
c Estimated based on 10-year survivors.
d Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
e The values given exclude the period within 5 years of first treatment.
f Based on national mortality rates.
g 95% CI here.
h Dose–response analysis based on the number of treatment courses given.
i Calculated as [(obs – exp) x 10^4 / (PY x mean dose)] with Poisson-based confidence intervals.
j Based on national incidence rates.
k Relative to an unexposed comparison group. Amongst exposed patients, there was no statistically significantly trend in risk with a measure of cumulative exposure.
l Amount of Thorotrast administered.
m Relative to workers not monitored for any radionuclide.

3.22 Brain and Other Central Nervous System Tumours

3.22.1 General epidemiology

In the UK each year, around 4,400 new cases of malignant tumours of the brain and central nervous system (CNS) are diagnosed, accounting for under 2% of all cancers (Cancer Research UK, 2008). The age-standardised incidence is around 6 per 100,000 persons. Non-malignant tumours of these sites also occur in substantial numbers, with an incidence of around 2 per 100,000 persons, or one-third of that for malignant tumours (ONS, 2006). After a gentle decline from birth until adolescence, the incidence of brain and CNS tumours increases steadily with age (Preston-Martin et al, 2006). The most frequent subtype comprises gliomas, which have a wide spectrum of behaviour from the low grade pilocytic astrocytoma of childhood to high grade glioblastoma multiforme. The next most frequent tumours are meningiomas, which are usually benign. Substantial numbers of ependymomas (mostly malignant) and schwannomas (benign) also occur, while medulloblastoma and other embryonal tumours are the most frequent subtype among children after gliomas. Because of their location, considerable numbers of intracranial tumours are not biopsied and hence never given a histological diagnosis (Preston-Martin et al, 2006). Malignant tumours of these sites are somewhat more frequent in males than females, but meningiomas occur more often in females than in males (ONS, 2006). The recorded incidence of CNS tumours has risen over past decades, especially among the elderly, but much of the increase is probably due to improved detection and registration (Preston-Martin et al, 2006).

Several genetic syndromes carry an increased risk of intracranial and intraspinal tumours. Numerically, the most important are neurofibromatosis 1 (gliomas, especially of the optic nerves) and neurofibromatosis 2 (meningiomas and vestibular schwannomas) (Preston-Martin et al, 2006). Ionising radiation is the only established environmental risk factor for brain and other CNS tumours (Preston-Martin et al, 2006; Schwartzbaum et al, 2006). The possible roles of non-ionising radiation (notably in relation to mobile phones) and some infectious agents are highly controversial. N-nitroso compounds (nitrosamines and nitrosamides) have been hypothesised to cause brain tumours, but their role has not been established despite numerous epidemiological studies of brain tumours in relation to dietary, industrial and other sources of these compounds (Preston-Martin et al, 2006; Schwartzbaum et al, 2006). Meta-analysis of published studies has shown a strong inverse relationship between allergy, eczema or asthma and gliomas, but information on meningiomas in association with atopic conditions is limited and heterogeneous (Linos et al, 2007).

3.22.2 Findings from studies of radiation exposure

3.22.2.1 Informative studies and evidence for association and causality

Table 3.22 summarises findings from cohort and case–control studies of tumours of the brain and central nervous system among radiation-exposed groups, specifically for studies in which individual assessments of exposure were made. Based on the summary of strengths and limitations given in Tables 2.2 and 2.4, the Life Span Study is the most informative study on external low LET exposures. The Israeli tinea capitis study and the North American Childhood Cancer Survivor Study (CCSS), together with the tonsil irradiation study for acoustic neuroma, are most informative on the effects at higher dose levels, but it should be noted that radiation exposure in these studies was exclusively in childhood.

Based on data presented in Table 3.22, there is evidence of an association between radiation exposure and tumours of these sites. Nearly all the studies indicate that the risk of brain and other CNS tumours increases with increasing level of radiation exposure, suggesting that the association is causal. The risk estimates are probably consistent across studies, given the apparent modifying effect of age at exposure (see below). The Life Span Study (Preston et al, 2002b) and the Israeli tinea capitis study (Ron et al, 1988) agreed that the risk was highest for schwannoma. The Israeli tinea capitis study and the CCSS both found a higher risk for meningioma than for malignant tumours (Sadetzki et al, 2005; Neglia et al, 2006).

3.22.2.2 Estimates of radiation risks

For external exposure, the best estimates are those given by Preston et al (2002b) based on the Life Span Study, namely an ERR at 1 Sv of 1.2 (95% CI 0.6, 2.1) for all CNS tumours, 0.6 (95% CI −0.2, 2.0) for glioma, 0.6 (95% CI −0.01, 1.8) for meningioma, and 4.5 (95% CI 1.9, 9.2) for schwannoma. The Life Span Study has also provided an estimated ERR at 1 Sv of 1.0 (95% CI −0.2, 3,5) for tumours of the pituitary, which is intracranial but not part of the CNS (Preston et al, 2002b). Of the two studies of internal high LET exposure in Table 3.22, the Portuguese Thorotrast study gave a relative risk of 2.94 (95% CI 0.91, 11.0) for systematically exposed patients relative to a group of unexposed patients and the UK nuclear industry workers study gave a relative risk of 0.89 (95% CI 0.46, 1.66) for workers monitored for exposure to plutonium relative to those not monitored for any radionuclide (Carpenter et al, 1998).

3.22.2.3 Modifying factors

The Life Span Study found consistently higher risks associated with exposure in the first 20 years of life compared with older ages specifically for schwannoma and meningioma and for all CNS tumours excluding schwannoma (Shore et al, 2002), although the effects were not statistically significant. There are indications from the most recent incidence follow-up of the Life Span Study that risks are largely if not entirely concentrated among males (Preston et al, 2007). This may be connected with the differences in histology between the sexes, with gliomas occurring much more frequently among males, and meningiomas being more frequent among females (Preston et al, 2007).

Both the UK NRRW (Muirhead et al, 2009) and the study of nuclear workers in 15 countries (Cardis et al, 2007) found no significant increase in risk for low dose exposure to adults, despite the large numbers of cases in each study. The Israeli tinea capitis study found a significant decline in ERR Gy^{-1} with increasing age at exposure for malignant brain tumours, but no trend with age for meningiomas (Sadetzki et al, 2005). In the CCSS, the ERR Gy^{-1} of glioma was higher for persons exposed before 5 years of age than for those exposed at older ages and was significantly different from zero only for the younger age group, whereas for meningioma the ERR Gy^{-1} was higher for persons exposed at age 5 years and above than for those exposed at younger ages (Neglia et al, 2006). In the Swedish pooled skin haemangioma study (Karlsson et al, 1998), there was a significant downward trend in ERR Gy^{-1} with age at exposure, with estimates of 4.5 for exposure before 5 months of age, 1.5 at 5–7 months and 0.4 thereafter. Dose-related risk estimates are not available for high dose exposures in adulthood. In a group of 426 patients who received radiotherapy for pituitary adenoma, virtually all of whom received a dose of at least 40 Gy, the relative risks compared to the general population were 10.5 (95% CI 4.3, 16.7) for all brain tumours, 7.0 (0.9, 13.1) for malignant brain tumours, and 24.3 (4.9, 43.8) for meningioma (Minniti et al, 2005). Comparison of these results with those for high dose exposure in childhood from the CCSS (Neglia et al, 2006) suggests that, as with lower dose exposures, the risks associated with high dose exposure in adulthood are lower than those in childhood.

TABLE 3.22 Risk estimates for incidence and mortality for brain and other central nervous system tumours from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only, except in the incidence data for the Life Span Study over 1958–95. For the Life Span Study analyses, the exposed group included survivors with organ doses of 0.005 Sv or more (weighted brain dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 95% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 95% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–95 (Preston et al, 2002b)						
	Schwannoma						
	Males	n.a.[a]	n.a.	n.a.	745,157	8.0 (2.7, 21)	n.a.
	Females	n.a.	n.a.	n.a.	1,244,140	2.3 (0.3, 7.0)	n.a.
	Age at exposure <20 y	n.a.	n.a.	n.a.	n.a.	6.0 (2.1, 14)	n.a.
	20–39 y	n.a.	n.a.	n.a.	n.a.	2.6 (<–0.2, 10)	n.a.
	≥ 40 y	n.a.	n.a.	n.a.	n.a.	3.3 (0.33, 11)	n.a.
	All ages and both sexes	55[b]	34.7	n.a.	1,989,297	4.5 (1.9, 9.2)	0.67 (0.3, 1.1)
	Nervous system other than schwannoma						
	Males	n.a.	n.a.	n.a.	745,157	1.4 (0.4, 3.3)	n.a.
	Females	n.a.	n.a.	n.a.	1,244,140	0.1 (–0.2, 0.9)	n.a.
	Age at exposure <20 y	n.a.	n.a.	n.a.	n.a.	1.2 (0.3, 2.9)	n.a.
	20–39 y	n.a.	n.a.	n.a.	n.a.	0.3 (<–0.2, 1.6)	n.a.
	≥ 40 y	n.a.	n.a.	n.a.	n.a.	0.1 (<–0.2, 1.2)	n.a.
	All ages and both sexes	173[b]	161.6	n.a.	1,989,297	0.6 (0.1, 1.4)	0.28 (–0.03, 0.7)
	All nervous system						
	All ages and both sexes	228[b]	196.3	n.a.	1,989,297	1.2 (0.6, 2.1)	n.a.
1.1	Life Span Study, 1958–98 (Preston et al, 2007)	137	n.a.	0.21	1,165,787	0.62 (0.21, 1.17)[c,d]	0.51 (0.17, 0.95)[c,d]

TABLE 3.22 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 95% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 95% CI)
3.1.1	New York tinea capitis (intracranial tumours) (Shore et al, 2003)	16	1.6	1.4	n.a.	5.6 (3.0, 9.4)	n.a.
3.1.2	Israel tinea capitis (Sadetzki et al, 2005)						
	Benign meningiomas	67	n.a.	1.38 median	427,000	4.63 (2.43, 9.12)	0.48 (0.28, 0.73)
	Malignant tumours	31	n.a.	1.38 median	428,000	1.98 (0.73, 4.69)	0.31 (0.12, 0.53)
3.1.4	Tonsil irradiation (acoustic neuroma) (Schneider et al, 2008)	43	n.a.	4.63	134,734	0.14 (0.0, 0.3)	n.a.
3.1.8	Swedish pooled skin haemangioma (Karlsson et al, 1998)	83	58	0.07	913,402	2.7 (1.0, 5.6)	2.1 (0.3, 4.41)
6.5	UK National Registry for Radiation Workers (malignant brain and CNS) (Muirhead et al, 2009) [e]	251	n.a.	0.025	2,388,848	−1.14 (−1.65, 0.16) [d]	n.a.
6.7	Chernobyl clean-up workers: Estonia and Latvia (Rahu et al, 2006)	9	4.1	0.11	113,194	*RR for >0.096 Sv vs <0.096 Sv* 0.52	n.a.
2.1.4	Brain tumours following childhood cancer (Little et al, 1998b)	12	n.a.	6.2	63,309	0.07 (<0, 0.62)	n.a.
2.1.7	CNS tumours following childhood cancer (Neglia et al, 2006)	116	n.a.	n.a.	n.a.	0.69 (0.25, 2.23)	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	9	n.a.	0.23	666,870	5.3 (1.4, 16) [d]	0.35 (0.13, 0.59) [d]
	Females	10	n.a.	0.21	1,061,690	0.51 (<−0.3, 3.9) [d]	0.04 (<−0.02, 0.2) [d]
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	235	n.a.	0.0194	5,192,710	<0	n.a.
6.5	UK National Registry for Radiation Workers (malignant brain and CNS) (Muirhead et al, 2009) [e]	217	n.a.	0.025	2,433.573	−1.00 (−1.78, 1.21) [d]	n.a.

TABLE 3.22 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose	Person-years of follow-up	Relative risk (with 95% CI)
INTERNAL HIGH LINEAR ENERGY TRANSFER EXPOSURES						
Mortality						
12.1	German Thorotrast patients (Becker et al, 2008)	19 (male) 17 (female)	n.a.	20.6 ml [f]	n.a.	Males 3.3 (1.3, 9.2) Females 17 (2.7, 711)
12.3	Portuguese Thorotrast patients (brain) (dos Santos Silva et al, 2003) [g]	10	0.76 [h]	20 ml [i] median	13,283	2.94 (0.91, 11.0) [j]
13.3.1	UK nuclear industry workers monitored for exposure to plutonium (Carpenter et al, 1998)	17	22.4 [h]	n.a.	n.a.	0.89 (0.46, 1.66) [k]

Notes
a Not available.
b Includes survivors with organ doses less than 0.005 Sv.
c Value applies at attained age 70 years following exposure at age 30 years.
d 90% CI here.
e Numbers calculated by NRRW investigators specifically for this document.
f Amount of Thorotrast administered.
g Based on follow-up and deaths 5 years or more following the first examination.
h Based on national mortality rates.
i Amount of Thorotrast administered.
j Relative to a group of unexposed patients, among whom 5 deaths occurred compared with 1.11 expected.
k Relative to workers not monitored for any radionuclide.

There was limited consistency between studies regarding the modifying effect of sex on radiation-associated risk. In the Life Span Study, there was a borderline positive effect of male sex for CNS tumours excluding schwannoma (Preston et al, 2002b). The Swedish pooled skin haemangioma study found a borderline significant ($p = 0.07$) positive effect of male sex for all intracranial tumours combined (Karlsson et al, 1998). The Israeli tinea capitis study found no evidence of differences in risk between males and females for malignant tumours or meningiomas (Sadetzki et al, 2005). The CCSS found no significant difference in risk of glioma between the sexes (Neglia et al, 2006).

A recent study of familial occurrence of meningioma in Israel supported the idea of varying genetic susceptibility to radiation-induced meningioma (Flint-Richter and Sadetzki, 2007). In the French–British study of brain tumours following childhood cancer, the risk was significantly increased for subjects who had received radiotherapy for a first CNS tumour or who had neurofibromatosis (Little et al, 1998b).

3.22.2.4 Gaps in knowledge

While several studies suggest that risk is higher for males than for females, the evidence to date is inconclusive. Work in progress to model radiation-related brain tumour risk is expected to provide further information on the possible heterogeneity of risk between the sexes, especially for exposure in adulthood. There is little information on dose-related risk of higher dose external exposure in adulthood, and this is unlikely to change without studies involving large numbers of persons, a wide range of doses and long follow-up. There is also rather little information on the effect of internal exposure.

3.23 Thyroid

3.23.1 General epidemiology

Thyroid cancer is one of the least frequent causes of death from cancer. In the general population, it accounts for approximately 1% of total cancer incidence (Parkin et al, 2002). Thyroid carcinomas are about three times more frequent in females than in males, suggesting a possible role of hormonal factors in thyroid cancer aetiology. Incidence of this disease is particularly elevated in Iceland and Hawaii, where the rate is nearly twice that in North European countries and in North America. In Hawaii, the incidence rate of thyroid cancer in all ethnic groups is higher than in the same ethnic group living in their country of origin, most probably due to differences in environmental, particularly dietary, exposures.

Thyroid tumours are rare in children (less than 1 case per 1,000,000 annually in most developed countries); the age-specific incidence rates increase rapidly with age. In the past three decades, incidence rates have been increasing in most developed countries, while mortality rates have been slowly decreasing. In the UK, age-standardised incidence rates among females increased from 2.6 to 3.6 per 100,000 population between 1995 and 2004, while male incidence rates remained around 1.4 per 100,000 population over the same period. Age-standardised mortality rates per 100,000 population in 2005 in the UK were 0.3 for males and 0.5 for females (Cancer Research UK, 2008).

Experimental studies have shown that long-term stimulation of the thyroid gland by thyroid-stimulating hormone, such as results from iodine deficiency, can lead to tumour formation with or without addition of a mutagenic agent (Thomas and Williams, 1991). Animal experiments indicate that iodine deficiency is a potent promoter of thyroid carcinogenesis (Ohshima and Ward, 1984, 1986) and that iodine excess may play a role in tumour promotion (Kanno et al, 1992). In humans, the evidence for a relationship between thyroid carcinoma risk and iodine status is less clear. Iodine deficiency is thought to be involved in the development of papillary thyroid cancer (PTC) because thyroid cancer mortality rates are high in mountainous areas, such as the Alps, Andes and Himalayas, where severe iodine deficiency was common. However, several high risk populations live on islands (such as Hawaii and Iceland), where iodine intake is generally high. The relationship between iodine intake and risk of thyroid cancer appears to be complex, since both deficiency and excess may inhibit the synthesis of thyroid hormones and cause goitre (Tavani et al, 1993). The two main types of thyroid carcinoma (papillary and follicular) may be linked to iodine-rich and iodine-deficient diets, respectively (Franceschi et al, 1989). Other dietary factors, including cruciferous and goitrogenic vegetables (Franceschi et al, 1990), may play a role in thyroid carcinogenesis.

3.23.2 Findings from studies of radiation exposure

The incidence of thyroid carcinoma, in particular PTC, has been shown to increase with external exposure to X-rays and gamma rays, in both epidemiological and experimental studies (Doniachi, 1963; Shore, 1992). The risk of radiation-induced cancer is considerably greater in those exposed as young children than as adults (Shore, 1992). In studies of the Life Span Study cohort of atomic bomb survivors, and of children exposed to ionising radiation for tinea capitis (Ron et al, 1989) and other benign disorders, the major increased risk is observed ten years or more after exposure and appears to follow a relative risk model with no decrease with time thereafter.

Before the Chernobyl nuclear plant accident, results of epidemiological studies of populations exposed to iodine-131 appeared to indicate a much smaller effect than that of external X-irradiation or gamma irradiation (Shore, 1992). The number of young people exposed in these studies was, however, very small, ranging between 127 and 3,500 in the different studies (Hamilton et al, 1987, 1989; Holm et al, 1988; Robbins et al, 1989; Rallison et al, 1990).

3.23.2.1 Informative studies and evidence for association and causality

The first part of Table 3.23 summarises findings from cohort and case–control studies of thyroid cancer among persons exposed to external radiation, specifically for studies in which individual assessments of exposures have been made. Among the atomic bomb survivors, the study that includes the largest number of cases of thyroid cancer, the ERR at 1 Sv was significantly elevated for exposures in adulthood: 0.57 among those exposed between 20 and 39 years of age and 0.27 for exposures later in life. The ERR at 1 Sv was also increased in a number of other studies, including those of Canadian radiation workers (Sont et al, 2001) and Chinese medical X-ray workers employed before 1970 (Wang et al, 2002), as well as in a study of patients treated with radiotherapy for Hodgkin disease (Hancock et al, 1991) and, though this is result is not statistically significant, in a nested case–control study in a cohort of survivors of childhood cancers (Boice et al, 1988). An increased risk was also seen, though dose estimates are not available, among radiological technologists who held patients during the X-ray procedure more than 50 times (Zabel et al, 2006). Although increases in the incidence of thyroid cancer have been reported in cohorts of Chernobyl clean-up workers (liquidators), analyses by level of officially recorded radiation doses were conducted in Russia, and no increased risk was observed (Ivanov et al, 2003).

The risk of radiation-induced cancer appeared to be consistently and considerably greater in those exposed as young children than as adults, with ERRs for external irradiation before the age of 20 ranging from 1 to 36 Gy^{-1} across studies (Table 3.23).

Table 3.23 also summarises findings from cohort and case–control studies of thyroid cancer among persons exposed to iodine isotopes in childhood, adolescence and adulthood. Much of the information comes from studies of the consequences of the Chernobyl accident where major efforts were made to reconstruct individual doses from iodine-131 (as well as, in some studies, from short-lived isotopes of iodine and tellurium and from long-lived radionuclides and external exposures) and to quantify uncertainties in dose estimates. Risk estimates from the large case–control studies in Belarus and Ukraine and from the cohort study in Ukraine are very close and similar, although slightly lower, to estimates from the pooled analysis of studies of external radiation (Ron et al, 1995). The ERR derived in the ecological study of Jacob et al (2006) is higher than those derived from the case–control and cohort studies.

TABLE 3.23 Risk estimates for thyroid cancer incidence from studies of radiation exposure (based on UNSCEAR, 2000)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv (weighted thyroid dose) or more for incidence. The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	48	n.a.[a]	0.26	436,180	0.49 (0.15, 1.15)[b]	0.5 (0.3, 1.5)[b]
	Females	217	n.a.	0.24	729,608	0.65 (0.27, 1.25)[b]	1.9 (1.3, 4.2)[b]
	Both sexes						
	Age at exposure < 20 y	105	n.a.	0.24	586,255	1.21 (0.43, 2.9)[c]	4.0 (1.7, 7.8)[c]
	20–39 y	87	n.a.	0.26	378,204	0.57 (0.24, 1.1)[c]	1.2 (0.5, 2.2)[c]
	40+ y	73	n.a.	0.24	201,330	0.27 (0.05, 0.77)[c]	0.4 (0.0, 1.3)[c]
	All	265	n.a.	0.25	1,165,788	0.57 (0.24, 1.1)[b]	1.2 (0.5, 2.2)[b]
–	Tuberculosis, adenitis screening (Hanford et al, 1962; Shore, 1992)						
	Age at exposure <20 y	6	0.0	8.20	950	36.5 (17.4, 69)[d]	9.3 (4.4, 17)[d]
	>20 y	2	0.2	8.20	3,100	1.2 (0.2, 3.7)	0.9 (0.1, 2.6)
6.4	Canadian National Dose Registry (Sont et al, 2001)	129	92.6	0.066	2,667,903	5.9 (2.5, 9.9)	2.1 (0.9, 3.4)
–	Chinese medical X-ray workers employed before 1970 (Wang et al, 2002)	13	6.32	0.551	357 753	1.9 (0.3, 4.4)	0.3 (0.15, 0.8)

TABLE 3.23 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
A6.19	Radiological technologists (Zabel et al, 2006)	121	n.a.	n.a.	n.a.	RR 1.47 (1.01, 2.15) [e] for holding patients for X-rays at least 50 times	n.a.
2.2.3	Cervical cancer case–control (Boice et al, 1988)	43	18.3 [f]	0.11	n.a.	12.3 (0.00, 76.0) [g]	6.87 (−2.04, 39.2) [h]
2.2.1	Cervical cancer cohort [g,i] (Boice et al, 1985)	16	12.5	0.11	342,786	2.5 (<0, 6.8)	0.9 (<0, 2.5)
2.2.12	Hodgkin disease patients (Hancock et al, 1991)	6	0.4 [j]	45	17,700	0.3 (0.1, 0.7)	0.07 (0.03, 0.1)
6.7	Chernobyl clean-up workers: Estonia and Latvia (Rahu et al, 2006)	7	0.99	0.11	113,194	*RR for >0.096 Sv vs <0.096 Sv* 0.84	n.a.
6.8	Chernobyl clean-up workers: Belarus, Russia and Ukraine (Ivanov et al, 2002, 2008)	67			1,117,740	0.48 (−1.93, 5.69) [e] (10 year latency)	
	Cohort studies of children						
1.1	Life Span Study, 1958–98 Age at exposure <20 y (Preston et al, 2007)	105	n.a.	0.24	586,255	1.21 (0.43, 2.9) [k]	4.0 (1.7, 7.8) [k]
2.1.1	Childhood cancer (Tucker et al, 1991) [l]	23	0.4	12.5	50,609	4.5 (3.1, 6.4)	0.4 (0.2, 0.5)
2.1.6	Childhood Cancer Survivor Study (Sigurdson et al, 2005; Ronckers et al, 2006)	63	n.a.	1.5–36.3 [m]	n.a.	1.31 [n]	n.a.
3.1.2	Israel tinea capitis (Sadetzki et al, 2006) [o]	103	n.a.	0.093	487,233	20.2 (11.8, 32.3) [e]	9.9 (5.7, 14.7) [e]
3.1.3	Rochester thymic irradiation (Shore et al, 1993) [p]	37	2.7	1.4	82,204	9.5 (6.9, 12.7)	3.0 (2.2, 4.0)

TABLE 3.23 ***continued***

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
3.1.8	Stockholm skin haemangioma (Lundell et al, 1994)	17	7.5 [q]	0.26	406,355	4.9 (1.3, 10.2)	0.9 (0.2, 1.9)
3.1.9	Gothenburg skin haemangioma (Lindberg et al, 1995)	15	8	0.12	370,517	7.5 (0.4, 18.1)	1.6 (0.09, 3.9)
	Screening studies of children						
3.1.4	Michael Reese Hospital tonsils (Schneider et al, 1993) [r]	309	110.4	0.6	88,101	3.0 (2.6, 3.5)	37.6 (32, 43)
3.1.5	Tonsils/thymus/acne screening (DeGroot et al, 1983; Shore, 1992)	11	0.2 [s]	4.5	6,800	12.0 (6.6, 20)	3.5 (2.0, 5.9)
3.1.6	Thymus adenitis screening (Maxon et al, 1980; Shore, 1992)	16	1.1 [o]	2.9	44,310	4.5 (2.7, 7.0)	1.2 (0.7, 1.8)
3.1.7	Lymphoid hyperplasia screening (Pottern et al, 1990; Shore, 1992) [t]	13	5.4 [o]	0.24	34,700	5.9 (1.8, 11.8)	9.1 (2.7, 18.3)
	Pooled analysis of five studies of children						
1.1, 3.1.2, 3.1.3, 3.1.4, 3.1.7	Life Span Study Israeli tinea capitis Rochester thymic irradiation Michael Reese Hospital tonsils Lymphoid hyperplasia screening	436	n.a.	n.a.	n.a.	7.7 (2.1, 28.7) [d]	4.4 (1.9, 10.1) [d]

TABLE 3.23 ***continued***

Study no.	Study	Observed cases	Expected cases	Mean dose (Sv)	Person-years	Excess relative risk at 1 Sv (with 95% CI)	Excess cumulative incidence per 100 persons at 1 Sv (with 95% CI)
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
	Studies of childhood exposure						
9.1.1	Belarus (Astakhova et al, 1998)	107	214	Median 0.106	n.a.	*Odds ratio ≥1 Gy vs <0.3 Gy* 5.04 (1.5, 6.7) to 5.84 (1.96, 17.3)	n.a.
9.1.2	Russian Federation – Bryansk (Davis et al, 2004a)	26	n.a.	Median 0.180 [u]	n.a.	4.2 (0.11, 23.5) [v]	n.a.
9.1.2	Russian Federation – Bryansk (Kopecky et al, 2006)	66	132	Median 0.020	n.a.	49.7 (5.8, 1152)	n.a.
–	Belarus and Ukraine – Ecological study (Jacob et al, 2004)	1,089	n.a.	0.002–0.5 depending on region	n.a.	18.9 (11.1, 26.7)	n.a.
9.1.3	Belarus and Russian Federation (Cardis et al, 2005a)	276	n.a.	Median 0.365 [w] (Belarus) 0.040 (Russia)	n.a.	*Up to 2 Sv:* 4.5 (1.2, 7.8) *Up to 1 Sv:* 5.6 (1.0, 10.1)	n.a.
9.1.4	Ukraine (Tronko et al, 2006)	45	n.a.	0.78 [v,x]	n.a.	5.25 (1.70, 27.5)	n.a.
9.3.1	Hanford (Davis et al, 2004b; Kopecky et al, 2004)	19	n.a.	0.174	n.a.	0.7 (95% CI n.a.)	0.2 (–0.1, 1.7)
A9.1	Marshall Islands (Takahashi et al, 2003)	50 (Bravo cohort)	n.a.	>0.150	n.a.	*Weighted dose on Utirik (with median) (mGy)* 0–34.1 (23.3) 34.2–74.7 (55.6) 74.8–187.1 (102.3) 187.2–6766.6 (770.0)	*Odds ratio (with 95% CI)* 1.00 0.99 (0.41, 2.42) 1.37 (0.59, 3.14) 1.67 (0.73, 3.83)

TABLE 3.23 ***continued***

Study no.	Study	Observed cases	Expected cases	Mean dose (Sv)	Person-years	Excess relative risk at 1 Sv (with 95% CI)
	Studies of adults					
8.1	Diagnostic iodine-131 (Dickman et al, 2003)	129	61.8	1.1	886,618	n.a.[y]
8.2	Diagnostic iodine-131 (Hall et al, 1996)	67	49	1.1	653,093	SIR 1.35 (1.05, 1.71)
8.3	Hyperthyroid patients (Ron et al, 1998)	24	n.a.	n.a.	738,831	SIR 3.94 (2.52, 5.86)
8.4	Hyperthyroid patients (Franklyn et al 1999)	9	2.8	n.a.	72,073	SIR 3.25 (1.69, 6.25)

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years.
d Values from UNSCEAR (2008), Table 39.
e 95% CI here.
f Calculated as the ratio of the observed cases to the estimated relative risk.
g Estimated based on 10-year survivors.
h Calculated using incidence rates estimated for non-exposed women in the cohort study of Boice et al (1985).
i Excludes cases diagnosed during first 10 years of follow-up.
j Based on rates from the Connecticut Tumor Registry.
k Gender-averaged risk estimate at attained age 70 years after exposure at age 10 years.
l Based on cohort members with 15 or more years of follow-up and population-expected rates.
m Range of mean thyroid doses for controls, according to type of the first cancer.
n Fitted value at 1 Sv, based on a linear-exponential dose–response model.
o Doses to the thyroid in this study may be much more uncertain than doses to organs directly in the X-ray beam.
p Known dose. Person-years and expected number of cases estimated from data given by Shore (1992).
q Based on cancer incidence rates for Stockholm.
r Study includes no unexposed controls; estimates of the number of expected cases were computed using the fitted ERR reported by Schneider et al (1993). Results are based on the new dosimetry described by the authors. The large EAR in this study illustrates the impact of screening on thyroid cancer risk estimates. As described by Schneider et al (1993), a special thyroid screening programme in this cohort was initiated in 1974. This screening led to a large increase in the number of incident cases detected among both cases and controls. The paper describes an analysis in which allowance was made for the effect of screening. The screening-adjusted EAR was estimated to be 1.7 $(10^4 \text{ PY Gy})^{-1}$.
s Expected number of cases estimated from data given by Shore (1992).
t This was a study of nodular disease, and cancer cases were not confirmed.
u Value for controls. Assumed here that 1 Sv = 1 Gy.
v Based on the fit of a log-linear dose–response model.
w Original findings expressed in terms of Gy. Assumed here that 1 Sv = 1 Gy.
x Value for cohort after excluding those persons with thyroid cancer.
y No evidence found of a relationship between risk and internal dose among either patients with or patients without prior exposure to external radiotherapy.

A very large ERR Sv^{-1} was estimated in a case–control study in the Bryansk area of Russia, based on small numbers of cases (Kopecky et al, 2006); doses in this study tended to be low, however, and estimates of risk at 1 Sv are therefore relatively uncertain.

Although individual dose estimates are not available, a 'dose-proxy' related trend was seen among those exposed to iodine-131 in childhood in the Marshall Islands (Takahashi et al, 2001), where some children are reported to have received very high doses (several tens of gray to the thyroid). No increased risk was

seen, however, in populations exposed to iodine-131 from environmental releases from the Hanford plant – based on 19 cases (Davis et al, 2004) or from fallout from the Nevada nuclear test site, based on 8 cases (Lyon et al, 2006).

Little information is available on the risk of thyroid cancer following iodine-131 exposure as an adult. A number of studies (summarised in Table 3.23) have noted an increased standardised incidence ratio in hyperthyroid patients treated with iodine-131 and in patients who received diagnostic iodine-131 exposures. No information is available, however, to quantify radiation doses.

Epidemiological studies of populations exposed to radiation in childhood or adolescence provide clear and fairly consistent evidence for an association between radiation exposure and thyroid cancer. Furthermore, taking into account the consistency of findings across studies and the clear dose–response relationships found, it can be concluded that this association is causal. Studies of populations exposed to external radiation in adulthood also provide evidence of an association, although the magnitude of the risk per sievert appears to be smaller than for exposures in childhood or adolescence.

3.23.2.2 Estimates of radiation risks

The vast majority of studies in which children or adolescents were exposed to external radiation or to iodine isotopes indicate that rates of thyroid cancer increase with increasing level of radiation dose. For external radiation, the best estimate of risk in relation to radiation exposure is that given by Ron and collaborators based on combined analyses of seven studies, namely an ERR of 7.7 Sv^{-1} (95% CI 2.1, 28.7). For iodine-131, the main analytical studies of the Chernobyl accident provide ERR estimates in the range 4 to 8 Gy^{-1}, statistically consistent with those derived from studies of external radiation, although these estimates are not, at present, adjusted for uncertainties in doses. The risk magnitude of the risk for exposure in adults is uncertain.

3.23.2.3 Modifying factors

Studies of external and internal exposures indicate that risks are considerably higher for exposures in childhood and adolescence. For external radiation, risk decreases rapidly with increasing age at exposure in childhood. For iodine-131, results of published studies are less consistent. There is some indication that iodine deficiency at the time of exposure may increase the risk of developing thyroid cancer among persons exposed to iodine-131 as children (Shakhatarin et al, 2003; Cardis et al, 2005a). Conversely, prolonged stable iodine supplementation in the years after exposure may reduce this risk (Cardis et al, 2005a). Further studies are needed to replicate these findings.

3.23.2.4 Gaps in knowledge

While the increased risk of thyroid cancer in those exposed in childhood and adolescence is well demonstrated, the magnitude of the effect of exposure on adults remains unclear. Studies of thyroid cancer among the Chernobyl clean-up workers, in whom an increased incidence of thyroid cancer has been reported, are nearing completion. For internal exposures, much of the information about risks comes from studies of iodine-131. The Belarus and Russian case–control study (Cardis et al, 2005a) – in which dose from different types of radiation was estimated – indicates that iodine-131 (which provided most of the dose to the thyroid for most study subjects) is mainly responsible for the increased risk after the Chernobyl accident. There is little power in that study to evaluate separately, however, the role of shorter-lived isotopes of iodine or tellurium or that of long-lived radionuclides.

3.24 All Solid Cancers Combined

Some epidemiological analyses have examined all solid cancers as a single group. As noted above, these diseases have diverse aetiologies and there are differences in their relationship with radiation exposure. However, there are some advantages to considering solid cancers in total, as follows.

a Certain studies have not presented results for specific types of cancer but rather for all solid cancers combined, usually because the data were too sparse to allow site-specific analyses.

b It may be difficult to discern an effect of radiation exposure on the risk of fairly rare types of cancer. However, the collective contribution from these cancer sites may well affect estimates of the total solid cancer risk from radiation.

c The statistical power of analyses to see how risks vary with radiation dose and how other factors might modify radiation risks would be greater when based on all solid cancers combined rather than on individual cancer sites. However, the possibility that such analyses might be affected by between-site differences needs to be borne in mind.

This section considers the findings that have been presented either for all solid cancers as a group or – if this information is not available – for all cancers other than leukaemia as a group, given that the evidence linking radiation to lymphomas is weak (AGIR, 2003; UNSCEAR, 2008).

The Life Span Study estimated the all solid cancer incidence relative risk for males at 1 Sv to be 0.35 (90% CI 0.28, 0.43) (Preston et al, 2007) at age 70 years following exposure at age 30 years, while the UK National Registry for Radiation Workers (UK NRRW) estimated the relative risk at 1 Sv to be 0.26 (90% CI 0.04, 0.51). Although the risk value based on the UK workers is smaller than that based on the Life Span Study it does lie within the confidence interval of the Life Span Study estimate, indicating reasonable agreement between these two large datasets. Other incidence studies reported in Table 3.24 have considerably wider confidence intervals.

Of the studies reporting all solid cancer mortality risk, the most powerful are again the Life Span Study, with a relative risk at 1 Sv of 0.37 (90% CI 0.26, 0.49) for males and 0.63 (90% CI 0.49, 0.79) for females, and the UK NRRW, with a combined relative risk at 1 Sv of 0.27 (90% CI 0.02, 0.56).

Jacob et al (2009) examined the risk of solid cancer in several populations exposed at low dose rates to cumulative doses from external low LET radiation of up to several hundred milligray. This analysis included results from the UK NRRW, as well as from studies of nuclear workers in other countries, Techa River residents and Chernobyl clean-up workers. The authors concluded that, both for incidence and mortality, the best estimate of the solid cancer ERR Gy^{-1} was similar to that for the Life Span Study. The ratio of the best estimate for the ERR Gy^{-1} from these studies relative to that in the Life Span Study, namely 0.98 (90% CI 0.41, 1.54) for incidence and 1.21 (90% CI 0.51, 1.90) for mortality, was borderline consistent with the dose and dose rate reduction factor (DDREF) of 2 proposed by the ICRP (2007) for use in radiological protection. The authors cautioned that "the value of the present study is a general estimation of implications of published studies rather than a quantitative risk evaluation", because they did not have access to individual-level data from the various studies.

TABLE 3.24 Risk estimates for incidence and mortality for all solid cancers from studies of radiation exposure (based on UNSCEAR, 2008)

The number of observed and expected cases as well as the mean dose and person-years for cohort studies are computed throughout this table for exposed persons only. In the Life Span Study the exposed group included survivors with organ doses of 0.005 Sv or more (weighted colon dose). The studies listed are those for which quantitative estimates of risk could be made

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
EXTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Incidence							
1.1	Life Span Study, 1958–98 (Preston et al, 2007)						
	Males	3,433	n.a. [a]	0.22	436,180	0.35 (0.28, 0.43) [b]	43 (33, 55) [b]
	Females	4,418	n.a.	0.21	729,608	0.58 (0.43, 0.69) [b]	60 (51, 69) [b]
	Both sexes						
	Age at exposure < 20 y	2,120	n.a.	0.22	586,255	0.67 (0.52, 0.85) [c]	90 (68, 113) [c]
	20–39 y	3,093	n.a.	0.21	378,204	0.47 (0.40, 0.54) [b]	52 (43, 60) [b]
	40+ y	2,638	n.a.	0.20	201,330	0.32 (0.24, 0.42) [d]	30 (22, 39) [d]
	All	7,851	n.a.	0.21	1,165,788	0.47 (0.40, 0.54) [b]	52 (43, 60) [b]
2.1.4	Childhood cancers (France/UK) (Guérin et al, 2007) [e]	123	n.a.	2 (median)	n.a.	0.13 (0.06, 0.28) [f,g]	n.a.
5.3	Prenatal exposure: survivors of atomic bombings (Preston et al, 2008)	94 *in utero* 649 early childhood	n.a.	n.a.	78,043 *in utero* 451,031 early childhood	1.0 (0.2, 2.3) [g] *in utero* 1.7 (1.1, 2.5) [g] early childhood (values are risk at age 50)	6.8 (<0, 49) [g] *in utero* 56 (36, 79) [g] early childhood (values are risk at age 50)
6.4	Canadian National Dose Registry (Sont et al, 2001) [h]	3,639	4,565	0.0066	2,667,903	2.3 (1.1, 3.9)	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	10,855	n.a.	0.025	2,388,848	0.266 (0.04, 0.51)	n.a.
6.8	Chernobyl clean-up workers: Russia (Ivanov et al, 2004, 2009)	1,370	n.a.	0.13	509,141	0.33 (−0.39, 1.22) [g,i] 0.2 (−0.4, 0.8) [g,j]	n.a.

TABLE 3.24 *continued*

Study no.	Study	Number of observed cases	Number of expected cases	Mean dose (Sv)	Person-years of follow-up	Excess relative risk at 1 Sv (with 90% CI)	Excess absolute risk per 10,000 persons per year at 1 Sv (with 90% CI)
9.2.1	Techa River population (Krestinina et al, 2007)	1,836 [k,l]	1,777 [m]	0.04 [n]	446,588	1.0 (0.3, 1.9) [g]	n.a.
Mortality							
1.2	Life Span Study, 1950–97 (Preston et al, 2003)						
	Males	4,451	n.a.	0.19	666,870	0.37 (0.26, 0.49)	12.6 (9.4, 16.2)
	Females	4,884	n.a.	0.18	061,690	0.63 (0.49, 0.79)	13.5 (7.4, 16.3)
3.3.1	Ankylosing spondylitis (Weiss et al, 1994) [f,o]	1,586	1,259 [p]	2.64	287,095	0.11 (0.04, 0.18) [g,q]	n.a.
6.1	Nuclear workers in Canada, UK, USA (Cardis et al, 1995) [f]	3,830	n.a.	0.0402	2124526	−0.07 (−0.39, 0.30)	n.a.
6.2	Nuclear workers in 15 countries (Cardis et al, 2005b, 2007)	4,770	n.a.	0.0194	5192710	0.87 (0.16, 1.71) [g]	n.a.
6.5	UK National Registry for Radiation Workers (Muirhead et al, 2009)	7,455	n.a.	0.025	2,433.573	0.27 (0.02, 0.56)	n.a.
6.9	Mayak workers (Shilnikova et al, 2003)	1,062 [r]	926.0	0.81 [s]	721,675	0.08 (0.03, 0.14) [t]	n.a.
7.1	Yangjiang background radiation (Sun et al, 2000; Tao et al, 2000)	677	684	0.0064 [u]	1,231,708	−0.11 (−0.67, 0.69) [g,v]	n.a.
9.3.1	Techa River population (Krestinina et al, 2005)	1,842 [w]	1,796 [x]	0.03 [n]	865,812	0.92 (0.2, 1.7) [g]	n.a.
INTERNAL LOW LINEAR ENERGY TRANSFER EXPOSURES							
Mortality							
9.4.1	Semipalatinsk cohort (Bauer et al, 2005)	532	n.a.	0.634 [y]	284,260	0.81 (0.46, 1.33) [g,z]	n.a.

TABLE 3.24 ***continued***

Notes

a Not available.
b Value applies at attained age 70 years following exposure at age 30 years.
c Value applies at attained age 70 years following exposure at age 10 years.
d Value applies at attained age 70 years following exposure at age 50 years.
e The values given here are for all second cancers, including cases of leukaemia and lymphoma.
f Dose–response analysis based on the number of treatment courses given.
g 95% CI here.
h The values given here are for all cancers other than leukaemia.
i Follow-up period 1991–2001 and using internal controls.
j Follow-up period 1991–2005 and using internal controls.
k All solid cancer excluding bone (Includes 81 deaths from haemato-lymphoetic malignancies among non-migrants and 14 among migrants).
l Based on 5-year latent period.
m Calculated based on a linear dose–response model.
n Value for stomach.
o The values given exclude the period within 5 years of first treatment.
p Based on national mortality rates.
q Dose–response analysis based on the number of treatment courses given.
r Solid cancers excluding lung, liver and skeleton.
s External gamma dose.
t Adjusted for plutonium exposures.
u Mean annual effective dose.
v Based on a 10-year latent period.
w Solid cancers excluding bone.
x Calculated based on a linear dose–response model.
y Average cumulative dose in the exposed group, arising from internal and external exposures.
z Based on a dose–response analysis conducted solely within the exposed group and with doses 70 mSv – 4 Sv.

3.24.1 Dose–response relationship

The Life Span Study supports the linear no-threshold dose response relationship for all solid cancers. This study cohort contains subjects with doses up to 4 Gy (although around 75% had doses in the range 0.005–0.2 Sv) and the linear dose–response relationship is heavily influenced by data at the upper end of the dose range. Analyses of the data excluding the highest doses (Little and Muirhead, 2000; Pierce and Preston, 2000) found that extrapolation of the linear dose–response relationship to low doses was in general appropriate. The effect of the adoption of a new dosimetry system, DS02, on the shape of the dose–response relationship was examined by Preston (2004). A statistically significant upward curvature of the solid cancer dose–response relationship was identified (based on subjects with doses between 0 and 2 Sv); however, due to its substantial divergence from the linear slopes indicated when doses of 0–1 Sv, 0–0.5 Sv and 0–0.25 Sv were used, it was not recommended for use in risk estimation.

The current Life Span Study data do not support a threshold below which radiation effects do not occur. However, if one were to exist, then Pierce and Preston (2000) suggest it must be less than 60 mSv, while in a later analysis (using a slightly longer period of follow-up) Preston et al (2003) suggest an upper limit for any threshold between 60 and 100 mSv. In the most recent analysis Preston et al (2007) lower the suggested upper limit further to 85 mSv.

3.24.2 Modifying effects of age and time

A large proportion of the Life Span Study cohort members who were exposed as children are still alive. Nevertheless, with increasing follow-up, it is becoming clear that the attained-age-specific relative risks for those exposed as children are higher than for those exposed as adults. Based on mortality data from the Life Span Study, Preston et al (2003) reported a 20% decrease in the attained-age-specific solid cancer ERR per decade increase in age at exposure. Additionally, for a particular age at exposure, the relative risk does not remain constant with time but decreases with increasing attained age. The ICRP, in Publication 103 (ICRP, 2007), also using Life Span Study data (with later follow-up), found a decrease of 31% per decade (from age 30 years) in the attained-age-specific solid cancer ERR based on mortality data but a decrease of 17% based on Life Span Study incidence data. These variations in risk with age and time indicate the importance of quantifying risks in terms of 'lifetime' risks rather than simply quoting relative or absolute risks at specific ages and times since exposure. While it is possible to examine the variation in risk with age and time for individual cancer types, the lack of sufficient data means that the uncertainties are much larger than those for all solid cancers together. Considerably more data will be required before it will be possible to use the Life Span Study to reliably distinguish differences in the pattern of risk with age and time between specific cancer types.

3.25 Conclusions

For many but not all solid cancers, there is epidemiological evidence of an association with ionising radiation exposure and, in most instances, this association is judged to be causal – specifically, for cancers of the oesophagus, stomach, colon, rectum, liver, lung, bone non-melanoma skin, breast (female), bladder and thyroid, together with brain and other central nervous system tumours (Table 3.25). For cancers of the salivary glands and ovary, the association is probably causal. The best estimate of the radiation-induced risk is generally based on incidence data from the Life Span Study. However, data from studies of medically exposed groups sometimes help to provide more pertinent estimates, particularly for rare cancers such as bone and non-melanoma skin, and for breast cancer in females where baseline rates differ considerably between Japan and Western countries.

There is some uncertainty – particularly for less common cancers where data are more sparse – about how radiation risks vary with factors such as sex, age at exposure and time since exposure. Also, information for specific cancers on risks from protracted and low doses is limited, owing to low statistical power. In addition, whilst there is information on the effects of high LET radiations for some cancers such as lung, liver and bone, for most cancers the epidemiological data are insufficient to provide direct estimates of risks from these radiations.

It is unclear whether cancers of the pancreas, connective tissue, melanoma of skin, uterine cervix, body of uterus, prostate, testis and kidney can be induced by radiation. In general, the data for these cancers are too sparse to assess consistency across studies, and the possibility of a small raised risk cannot be ruled out.

TABLE 3.25 Assessment by cancer site of the evidence for associations with ionising radiation exposure and best estimates of relative risk

Cancer site	Is there evidence for an association?	Is any association likely to be causal?	Best estimate of the relative risk at 1 Sv	Best estimate of the excess relative risk [a] for an additional 1 Sv	Source of risk estimate	Comments
Salivary glands	Yes	Probably	2.8 (90% CI 1.6, 5.0)	1.8 (90% CI 0.6, 4.0)	Life Span Study (incidence data)	Little information on potential modifying factors Unclear whether other types of oral cancer are associated with radiation
Oesophagus	Yes	Yes	1.52 (90% CI 1.15, 2.0)	0.52 (90% CI 0.15, 1.0)	Life Span Study (incidence data)	Variations in the relative risk with age at exposure and attained age may be similar to those for other solid cancers, but the available data lack power to indicate such trends
Stomach	Yes	Yes	1.34 (90% CI 1.22, 1.47) [b]	0.34 (90% CI 0.22, 0.47) [b]	Life Span Study (incidence data)	Relative risks appear to be more comparable than absolute risks across studies Relative risk decreases and excess absolute risk increases with increasing attained age
Colon	Yes	Yes	1.54 (90% CI 1.30, 1.81) [b]	0.54 (90% CI 0.30, 0.81) [b]	Life Span Study (incidence data)	While the results from the Life Span Study show a clear risk and a dose–response, the inconsistencies in the results from studies of medical exposures remain unresolved There is little information on risks related to high LET radiation
Rectum	Yes	Yes	1.19 (90% CI 0.96, 1.47)	0.19 (90% CI −0.04, 0.47)	Life Span Study (incidence data)	Given the clear association between radiation and colon cancer risk, the association seen in the Life Span Study, though not significant, may be real. The magnitude of the association is unclear and, if any, is weaker than for colon cancer There is little evidence on risks associated with internal high or low LET radiation
Liver	Yes	Yes	1.30 (90% CI 1.11, 1.55) [b]	0.30 (90% CI 0.11, 0.55) [b]	Life Span Study (incidence data)	Little or no evidence of excess risk in individuals exposed before 10 years of age Suggestion of multiplicative effect of hepatitis C viral infection on radiation risk

TABLE 3.25 *continued*

Cancer site	Is there evidence for an association?	Is any association likely to be causal?	Best estimate of the relative risk at 1 Sv	Best estimate of the excess relative risk [a] for an additional 1 Sv	Source of risk estimate	Comments
Pancreas	Unclear	Unclear	1.26 (90% CI 0.93, 1.68)	0.26 (90% CI −0.07, 0.68)	Life Span Study (incidence data)	Gap in knowledge is mainly due to small number of cases
Trachea, bronchus and lung	Yes	Yes	External exposure: 1.81 (90% CI 1.56, 2.1) [c] Radon: 1.16 (95% CI 1.05, 1.31) at 100 Bq m^{-3}	External exposure: 0.81 (90% CI 0.56, 1.1) [c] Radon: 0.16 (95% CI 0.05, 0.31) for an additional 100 Bq m^{-3} [c]	Life Span Study (incidence data) European pooling of indoor radon studies	Apparent heterogeneity in findings across studies of external exposure, probably due to an inability to treat smoking adequately in analyses. In contrast, findings from studies of indoor radon – for which detailed smoking data are available – are remarkably consistent
Bone	Yes	Yes	1.19 (95% CI 1.14, 1.32)	0.19 (95% CI 0.14, 0.32)	Patients given radiotherapy for malignant disease	The studies of incidence in radiotherapy patients seem to be consistent with each other. The studies of TB/ankylosing spondylitis patients and US radium luminisers include large numbers of cases, but risk estimates are hard to find and consistency may thus be impossible to assess
Connective tissue	Unclear	Unclear	n.a. [d]	n.a.		
Melanoma of skin	Unclear	Unclear	n.a.	n.a.	n.a.	Data too sparse to assess consistency across studies
Non-melanoma skin	Yes	Yes	1.6 (95% CI 1.3, 2.1)	0.6 (95% CI 0.3, 1.1)	New York tinea capitis patients (whites)	Relative risk decreases with increasing age at exposure Uncertainty in the shape of the dose response for basal cell carcinoma below 1 Sv Little information on whether the ionising radiation related risk of either basal cell or squamous cell carcinoma is modified by UVR exposure
Breast (female)	Yes	Yes	1.74 (95% CI 1.4, 2.2) [e]	0.74 (95% CI 0.4, 1.2) [f]	Combined analysis of Life Span Study and several medically exposed cohorts	Uncertainty remains about the most appropriate form of risk model and about modifying effects

TABLE 3.25 *continued*

Cancer site	Is there evidence for an association?	Is any association likely to be causal?	Best estimate of the relative risk at 1 Sv	Best estimate of the excess relative risk [a] for an additional 1 Sv	Source of risk estimate	Comments
Uterine cervix	Unclear	Unclear	n.a.	n.a.	n.a.	Data too sparse to assess consistency across studies. Study limitations, certainly on size, are very important
Body of uterus	Unclear	Unclear	n.a.	n.a.	n.a.	Data too sparse to assess consistency across studies. Study limitations, certainly on size, are very important
Ovary	Yes	Probably	1.61 (90% CI 1.00, 2.5)	0.61 (90% CI 0.00, 1.5)	Life Span Study (incidence data)	Data too sparse to assess consistency across studies. Study limitations, certainly on size, are very important
Prostate	Unclear	Unclear	1.11 (90% CI 0.90, 1.54)	0.11 (90% CI −0.10, 0.54)	Life Span Study (incidence data)	There remains no definite evidence as to whether radiation exposure is associated with a risk of prostate cancer There is little information on the risks associated with internal high or low LET radiation
Testis	Unclear	Unclear	n.a.	n.a.	n.a.	Data too sparse to assess consistency across studies
Bladder	Yes	Yes	2.23 (90% CI 1.59, 3.1) [b]	1.23 (90% CI 0.59, 2.1) [b]	Life Span Study (incidence data)	No statistically significant variations in relative risk by age at exposure, time since exposure or attained age Potential interactions between smoking and radiation are not known
Kidney	Unclear	Unclear	1.13 (90% CI 0.75, 1.75)	0.13 (90% CI −0.25, 0.75)	Life Span Study (incidence data)	Little information on radiation and kidney cancer, including potential modifying effects (eg by age or sex)

TABLE 3.25 *continued*

Cancer site	Is there evidence for an association?	Is any association likely to be causal?	Best estimate of the relative risk at 1 Sv	Best estimate of the excess relative risk [a] for an additional 1 Sv	Source of risk estimate	Comments
Brain and other central nervous system (malignant and benign tumours)	Yes	Yes	1.62 (90% CI 1.21, 2.2) [b]	0.62 (90% CI 0.21, 1.2) [b]	Life Span Study (incidence data)	Risk estimates are probably consistent across studies, given that age at exposure varies greatly between studies and risk appears to decline with age at exposure Little information on internal exposure
Thyroid	Yes	Yes	8.7 (95% CI 3.1, 29.7) for exposure at ages less than 15 years	7.7 (95% CI 2.1, 28.7) for exposure at ages less than 15 years	Combined analysis of Life Span Study and several medically exposed cohorts	Findings from studies of external exposure at ages less than 15 years are generally consistent Post-Chernobyl studies give ERR estimates from iodine-131 exposures that are consistent with those from external exposure, although the former estimates have not been adjusted for doses uncertainties Studies of both external and internal exposure indicate that risks decrease with increasing age at exposure

Notes

a The excess relative risk is equal to the relative risk minus one. A relative risk of one (or equivalently an excess relative risk of zero) corresponds to no effect of radiation.

b Value applies at attained age 70 years following exposure at age 30 years.

c This excess relative risk is based on studies in Europe and incorporates an adjustment for smoking. As stated in Section 3.9, this value equates to an ERR of 2.07 Sv^{-1} based on effective dose.

d Not available.

e Value applies at an attained age of 50 years.

4 Risk to the UK Population

4.1 Introduction

In the previous chapter we identified those cancer sites that may be induced by radiation. A summary was presented in Table 3.25. In this chapter we would like to formulate risk models that would quantify the relationship between radiation dose and risk for each of these cancer sites. However, it takes a large amount of highly informative data to identify a dose–response relationship, particularly when, as in this case, the cancer-causing effect is likely to be small at dose levels to which humans are commonly exposed.

The most comprehensive source of information from which to derive a dose–response relationship is the Life Span Study of the Japanese atomic bomb survivors. For many of the cancer sites identified in Table 3.25, the Life Span Study data can be used to estimate risks. Unfortunately, for some sites there is insufficient information in the Life Span Study to be able to estimate a site-specific risk. For these sites, a generic risk measure can be derived by combining the data for all solid cancer sites other than those for which the Life Span Study has sufficient information to generate an individual model.

In the first part of this chapter we aim to estimate the risk of cancer, other than cancers of the blood or lymphatic system, for the general UK population, arising from exposure to ionising radiation. Risks are calculated for ten specific cancer sites and for a group consisting of all other sites. In the second part of the chapter these values are used to quantify the risk associated with specific typical exposures such as mammography and CT colonography.

It is not in the remit of this report to calculate the total radiation-induced cancer burden for the UK population. However, the information provided in the first part of the chapter, along with information on exposures of the UK population (see, for example, Jones et al, 2007), would enable estimates to be made.

4.2 Methodology

Various measures of population cancer risk have been adopted in assessments of radiation risks. These include:

Excess Cancer Deaths per unit exposure (ECD) – the difference between the lifetime risk of death in an exposed population and the lifetime risk of death in a similar, unexposed population

Excess Cancer Incidence per unit exposure (ECI) – the difference between the lifetime risk of cancer incidence in an exposed population and the lifetime risk of cancer incidence in a similar, unexposed population

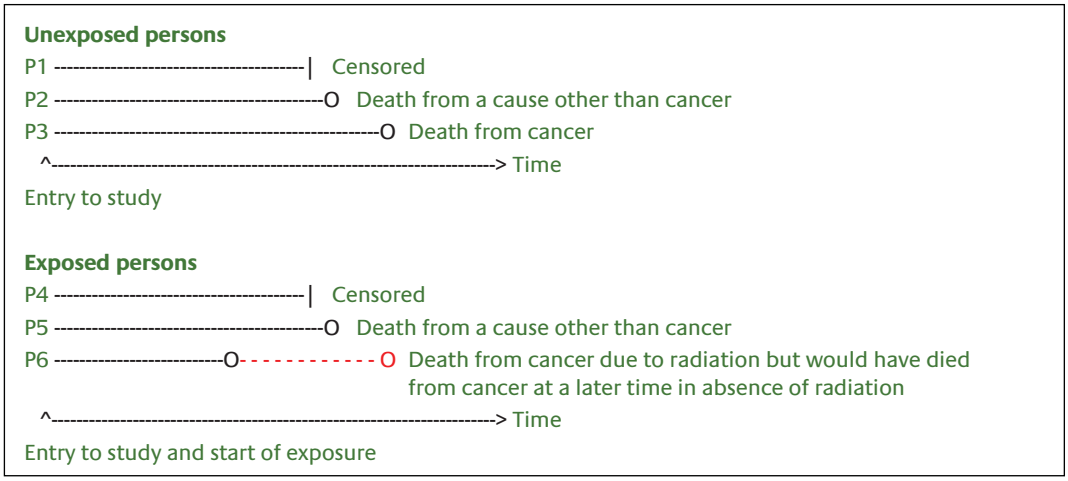
A proportion of those people who develop a radiation-induced cancer would have developed a cancer anyway at a later point in life regardless of their radiation exposure. The ECD and ECI measures exclude these radiation-induced cancers and thus underestimate the true risk of radiation exposure. Two further measures that do take these cancers into account are:

Risk of Exposure-Induced Death per unit exposure (REID)

Risk of Exposure-Induced Cancer incidence per unit exposure (REIC)

The difference between the ECD and REID (or equivalently between the ECI and REIC) can be illustrated using the following example.

Consider a study with three exposed persons and three non-exposed persons



In this extreme situation, after everyone has left the study (died or censored), the excess lifetime risk of cancer is zero, because the same number of people died from cancer in these two groups of equal size. However, the number of exposure-induced deaths is one. The difference between the measures arises from the way in which person P6 is classified: the ECD ignores the early occurrence of this death due to radiation exposure, but the REID does not.

In practice, the differences between the ECD and REID and between the ECI and REIC are small, particularly when considering rare cancers. However, where differences do exist, it is generally preferable to use the REID or REIC, since they include deaths and cases, respectively, that would have occurred anyway but earlier than would have been expected without the radiation exposure.

A fifth measure of risk is

Years of Life Lost if Radiation-Induced Cancer death occurs (years of life lost per radiation-induced cancer death) (YLLRIC)

More detailed definitions of these measures are given in Appendix A.

The measures of risk described above are derived for this report using data from the Life Span Study of the Japanese atomic bomb survivors. The detailed description of risks from other studies given in this report is provided principally to assess consistency between studies and to validate the use of the data from the Life Span Study. With a measure of cancer risk relating to a unit of radiation, and measures of exposures to ionising radiation in general contemporary life, it is possible to estimate the cancer risk associated with these general exposures. The principle is extremely simple, although the mathematical calculations can be complex.

The risk estimates (REID, REIC, ECD, ECI and YLLRIC) presented below were calculated using excess relative risk (ERR) models and excess absolute risk (EAR) models fitted to the Life Span Study mortality and incidence data, using the latest DS02 dosimetry and follow-up and a single acute dose of 0.1 Sv. It is assumed for the purpose of these calculations that this is a whole-body dose. However, at this level of dose, the risk from exposure of a particular organ is similar to the risk that would be calculated if only the relevant organ had been irradiated.

To calculate the risk estimates, values for the ERR and EAR based on linear-quadratic models, as described in Appendix B (expressions B8 and B9), were multiplied by the background age-, sex- and cancer-site-specific mortality rates for England and Wales in 2003 and the corresponding cancer incidence rates for 2001 (ONS, 2004a,b). In this way, annual cancer mortality and incidence radiation risk estimates were calculated for both sexes and each year following first exposure, up to an age of 100 years (assumed to represent a maximum lifetime).

Each annual risk was then multiplied by a measure of the probability that the person survives to each age following first exposure (the choice of survival function depending on which of the lifetime risk estimates is being considered, ie REID or ECD or their incidence equivalents). These annual measures were then summed to provide the lifetime risk measure for a given age at first exposure. This calculation was then repeated for each possible age at first exposure and an average value, weighted according to the numbers of people in the population at the different ages, was derived to provide an overall population measure of risk. The calculations were performed separately for males and females and an average value for both sexes combined was also calculated, based on the relative numbers of males and females in the population.

4.3 Radiation Risk Estimates for the General UK Population

Tables 4.1 and 4.2 show estimates of the absolute risks of excess lifetime cancer incidence (REIC), based on the ERR and EAR models, respectively. These calculations have been made for a population in equilibrium (ie with the underlying mortality rates and population structure of the current UK population) from various models fitted to Life Span Study incidence data (Preston et al, 2007) and assuming a uniform whole-body dose of 0.005 Sv. These tables show risks by cancer site, sex and several different ages at exposure, namely 0, 1, 2–4, 5–9, 10–14, ..., 80–84 and 85+ years.

TABLE 4.1 Absolute excess lifetime incidence risk by cancer site per 1000 people of either sex exposed to 0.005 Sv. Risk estimates for solid cancer incidence by age at exposure for the current UK population, assuming a test dose, D_t, of 0.005 Sv, using generalised ERR models. Details of fitted models are outlined in Appendix B

Risk estimates are calculated for a population in equilibrium (underlying mortality and incidence rates and population structure of the current (2001, incidence), (2003, mortality) UK population) from various models fitted to the Life Span Study incidence data (Preston et al, 2007). Risks are given as percentages

Age at exposure (years)	Radiation-induced excess cancer cases – males							Radiation-induced excess cancer cases – females							
	Bladder cancer	Colon cancer	Liver cancer	Lung cancer	Stomach cancer	Thyroid cancer	Leuk-aemia *	Bladder cancer	Colon cancer	Liver cancer	Lung cancer	Stomach cancer	Thyroid cancer	Leuk-aemia *	Breast cancer
0	0.161	1.568	0.003	0.014	0.003	0.032	0.090	0.017	0.070	0.000	0.032	0.004	0.031	0.085	0.157
1	0.151	0.839	0.003	0.014	0.003	0.032	0.055	0.016	0.071	0.000	0.032	0.004	0.025	0.052	0.158
2–4	0.132	0.270	0.003	0.014	0.003	0.033	0.025	0.016	0.071	0.000	0.033	0.004	0.019	0.022	0.158
5–9	0.092	0.044	0.003	0.015	0.003	0.034	0.013	0.014	0.032	0.000	0.034	0.004	0.013	0.010	0.158
10–14	0.067	0.022	0.002	0.016	0.003	0.036	0.010	0.013	0.007	0.000	0.036	0.003	0.009	0.007	0.158
15–19	0.058	0.019	0.002	0.016	0.003	0.038	0.008	0.011	0.006	0.000	0.038	0.003	0.007	0.006	0.159
20–24	0.051	0.018	0.002	0.018	0.003	0.041	0.007	0.011	0.005	0.000	0.041	0.003	0.005	0.005	0.160
25–29	0.045	0.017	0.002	0.019	0.003	0.044	0.007	0.010	0.005	0.000	0.044	0.003	0.003	0.005	0.158
30–34	0.040	0.016	0.002	0.021	0.003	0.049	0.006	0.009	0.005	0.000	0.049	0.003	0.002	0.005	0.152
35–39	0.036	0.016	0.002	0.023	0.003	0.055	0.006	0.009	0.005	0.000	0.055	0.003	0.002	0.004	0.141
40–44	0.032	0.015	0.002	0.027	0.003	0.062	0.006	0.009	0.004	0.000	0.062	0.003	0.001	0.004	0.126
45–49	0.029	0.014	0.002	0.030	0.003	0.069	0.006	0.009	0.004	0.000	0.069	0.003	0.001	0.004	0.107
50–54	0.027	0.013	0.002	0.034	0.002	0.075	0.005	0.009	0.003	0.000	0.075	0.003	0.001	0.004	0.085
55–59	0.024	0.011	0.001	0.037	0.002	0.080	0.005	0.009	0.003	0.000	0.080	0.002	0.000	0.003	0.065
60–64	0.022	0.009	0.001	0.038	0.002	0.082	0.005	0.009	0.002	0.000	0.082	0.002	0.000	0.003	0.050
65–69	0.019	0.007	0.001	0.036	0.002	0.078	0.004	0.009	0.002	0.000	0.078	0.002	0.000	0.003	0.038
70–74	0.016	0.005	0.001	0.030	0.001	0.061	0.003	0.008	0.001	0.000	0.061	0.001	0.000	0.002	0.028
75–79	0.012	0.003	0.000	0.021	0.001	0.039	0.003	0.007	0.001	0.000	0.039	0.001	0.000	0.002	0.018
80–84	0.009	0.002	0.000	0.013	0.001	0.021	0.002	0.005	0.000	0.000	0.021	0.001	0.000	0.001	0.011
85+	0.004	0.001	0.000	0.007	0.000	0.010	0.001	0.003	0.000	0.000	0.010	0.000	0.000	0.001	0.005

* Leukaemia risk estimates based on models from Little et al (2008) are provided to enable total cancer risks to be calculated.

TABLE 4.2 Absolute excess lifetime incidence risk by cancer site per 1000 people of either sex exposed to 0.005 Sv. Risk estimates for solid cancer incidence by age at exposure and years after exposure for the current UK population, assuming a test dose, D_t, of 0.005 Sv, using generalised EAR models. Details of fitted models are outlined in Appendix B

Risk estimates are calculated for a population in equilibrium (underlying mortality and incidence rates and population structure of the current (2001, incidence), (2003, mortality) UK population) from various models fitted to the Life Span Study incidence data (Preston et al, 2007). Risks are given as percentages

Age at exposure (years)	Radiation-induced excess cancer cases – males							Radiation-induced excess cancer cases – females							
	Bladder cancer	Colon cancer	Liver cancer	Lung cancer	Stomach cancer	Thyroid cancer	Leuk-aemia *	Bladder cancer	Colon cancer	Liver cancer	Lung cancer	Stomach cancer	Thyroid cancer	Leuk-aemia *	Breast cancer
0	0.082	0.017	0.016	0.014	0.020	0.019	0.009	0.010	0.009	0.002	0.024	0.027	0.050	0.005	0.109
1	0.080	0.018	0.016	0.014	0.020	0.017	0.009	0.010	0.009	0.002	0.024	0.027	0.047	0.005	0.106
2–4	0.075	0.018	0.016	0.014	0.020	0.015	0.009	0.009	0.009	0.002	0.024	0.027	0.041	0.005	0.099
5–9	0.065	0.017	0.016	0.014	0.020	0.012	0.009	0.008	0.009	0.002	0.024	0.027	0.033	0.005	0.087
10–14	0.055	0.017	0.016	0.014	0.020	0.009	0.008	0.007	0.009	0.002	0.024	0.027	0.025	0.005	0.072
15–19	0.046	0.017	0.016	0.014	0.020	0.007	0.008	0.007	0.009	0.002	0.024	0.027	0.020	0.005	0.060
20–24	0.038	0.017	0.016	0.014	0.020	0.006	0.008	0.006	0.009	0.002	0.024	0.026	0.016	0.004	0.050
25–29	0.032	0.017	0.016	0.014	0.020	0.004	0.007	0.005	0.008	0.002	0.024	0.026	0.012	0.004	0.040
30–34	0.026	0.016	0.016	0.014	0.019	0.004	0.007	0.004	0.008	0.002	0.024	0.026	0.010	0.004	0.033
35–39	0.022	0.016	0.016	0.014	0.019	0.003	0.006	0.004	0.008	0.001	0.023	0.025	0.008	0.004	0.026
40–44	0.018	0.015	0.015	0.013	0.018	0.002	0.006	0.003	0.008	0.001	0.023	0.025	0.006	0.003	0.020
45–49	0.014	0.014	0.014	0.013	0.017	0.002	0.005	0.003	0.007	0.001	0.023	0.024	0.005	0.003	0.015
50–54	0.011	0.013	0.013	0.013	0.016	0.001	0.005	0.002	0.007	0.001	0.023	0.023	0.004	0.003	0.011
55–59	0.009	0.011	0.012	0.012	0.015	0.001	0.004	0.002	0.006	0.001	0.022	0.021	0.003	0.003	0.008
60–64	0.007	0.010	0.010	0.011	0.014	0.001	0.004	0.002	0.005	0.001	0.021	0.019	0.002	0.002	0.006
65–69	0.005	0.008	0.009	0.010	0.012	0.001	0.003	0.001	0.004	0.001	0.019	0.017	0.002	0.002	0.004
70–74	0.004	0.006	0.007	0.009	0.009	0.000	0.003	0.001	0.003	0.001	0.016	0.014	0.001	0.002	0.002
75–79	0.003	0.005	0.005	0.007	0.007	0.000	0.002	0.001	0.002	0.001	0.013	0.011	0.001	0.001	0.001
80–84	0.002	0.003	0.003	0.005	0.005	0.000	0.002	0.001	0.002	0.000	0.010	0.007	0.000	0.001	0.001
85+	0.001	0.002	0.002	0.004	0.003	0.000	0.001	0.000	0.001	0.000	0.007	0.004	0.000	0.001	0.000

* Leukaemia risk estimates based on models from Little et al (2008) are provided to enable total cancer risks to be calculated.

Table 4.3 gives solid cancer mortality risk estimates for the whole population as a single group. It shows that, for each measure of risk, the differences between the results based on the relative and absolute risk models are small. The fact that the REID values are slightly larger than the ECD values is to be expected and is a consequence of the definitions of these measures. Table 4.4 presents the risks separately for seven categories of age at exposure.

TABLE 4.3 Absolute excess lifetime mortality risk per 100 people (males and females separately) exposed to 0.1 Sv

Risk estimates for solid cancer mortality by sex in the current UK population, using generalised ERR and generalised EAR models (all taken from Little et al, 2008, and UNSCEAR, 2008)

Model, modifying terms	Sex	Excess cancer deaths (ECD) (mean, with 95% CI [c])	Radiation-induced cancer deaths (REID) (mean, with 95% CI [c])	Years of life lost if radiation-induced cancer death occurs (YLLRIC) (mean, with 95% CI [c])
ERR [a]	Males	0.35 (0.15, 0.60)	0.44 (0.19, 0.76)	12 (11, 14)
	Females	0.55 (0.27, 0.86)	0.64 (0.32, 1.01)	15 (13, 17)
	Both	0.45 (0.22, 0.71)	0.54 (0.27, 0.85)	14 (13, 16)
EAR [b]	Males	0.31 (0.12, 0.55)	0.39 (0.15, 0.70)	14 (13, 16)
	Females	0.44 (0.19, 0.70)	0.51 (0.22, 0.82)	15 (13, 16)
	Both	0.37 (0.16, 0.61)	0.45 (0.19, 0.73)	15 (13, 16)

Notes

a ERR = $\alpha_s(D+\beta D^2)\,(a-e)^{\kappa}\,a^{\tau}$, as per model B8 (Appendix B), where a = attained age, e = age at exposure and s = sex.

b EAR = $\alpha(D+\beta D^2)\,(a-e)^{\kappa}\,a^{\tau}$, as per model B9 (Appendix B), where a = attained age and e = age at exposure.

c CI = Bayesian confidence interval.

Table 4.5 presents incidence risks, using the same models as in Tables 4.1 and 4.2, but for all ages at exposure, and giving estimates of uncertainty. A feature of Table 4.5 is the contrast between the risks estimated using the EAR and ERR models. For many cancer sites, in particular the oesophagus, lung, non-melanoma skin, breast and brain and central nervous system, risks estimated using the ERR models are very much greater than those estimated using the EAR models. This is not surprising: background rates of these cancers are very much lower in the Japanese population compared with that of the UK, so that transfer of relative risk will lead to very much greater risks than using an absolute risk model. For stomach cancer the opposite pattern is observed, and the reason for this is also unsurprising, namely the very much lower stomach cancer rates in the UK compared with Japan.

Table 4.6 presents a comparison of the risks of all solid cancers (considered as a single group) in this report with those derived in previous studies. It was not possible to include values from ICRP Publication 103 (ICRP, 2007), as no suitable comparison values were available from that report.

TABLE 4.4 Absolute excess lifetime mortality risk per 100 people of either sex exposed to 0.1 Sv

Risk estimates for solid cancer mortality by age-at-exposure group in the current UK population, using generalised ERR and generalised EAR models (all taken from Little et al, 2008, and UNSCEAR, 2008)

Model, modifying factors	Age at exposure	Excess cancer deaths (ECD) (mean, with 95% CI [c])	Radiation-induced cancer deaths (REID) (mean, with 95% CI [c])	Years of life lost if radiation-induced cancer death occurs (YLLRIC) (mean, with 95% CI [c])
ERR [a]	0–9	0.96 (0.45, 1.58)	1.17 (0.55, 1.92)	17 (14, 20)
	10–19	0.79 (0.38, 1.26)	0.95 (0.46, 1.52)	15 (13, 17)
	20–29	0.63 (0.31, 1.00)	0.77 (0.37, 1.20)	14 (13, 16)
	30–39	0.49 (0.23, 0.78)	0.59 (0.28, 0.93)	13 (12, 14)
	40–49	0.35 (0.16, 0.60)	0.42 (0.19, 0.71)	11 (10, 13)
	50–59	0.23 (0.09, 0.43)	0.28 (0.11, 0.51)	10 (9, 11)
	60–69	0.13 (0.04, 0.28)	0.15 (0.05, 0.32)	8 (7, 8)
	70+	0.04 (0.01, 0.10)	0.05 (0.01, 0.12)	5 (5, 6)
	All ages	0.45 (0.22, 0.71)	0.54 (0.27, 0.85)	14 (13, 16)
EAR [b]	0–9	0.68 (0.28, 1.15)	0.83 (0.34, 1.40)	17 (15, 19)
	10–19	0.60 (0.25, 0.98)	0.73 (0.31, 1.20)	16 (15, 18)
	20–29	0.51 (0.22, 0.83)	0.62 (0.27, 1.01)	15 (14, 17)
	30–39	0.42 (0.18, 0.70)	0.51 (0.21, 0.84)	14 (12, 16)
	40–49	0.33 (0.13, 0.56)	0.39 (0.16, 0.68)	12 (11, 14)
	50–59	0.24 (0.09, 0.44)	0.28 (0.10, 0.52)	10 (9, 11)
	60–69	0.15 (0.05, 0.31)	0.18 (0.06, 0.36)	8 (7, 8)
	70+	0.06 (0.02, 0.14)	0.07 (0.02, 0.16)	5 (5, 6)
	All ages	0.37 (0.16, 0.61)	0.45 (0.19, 0.73)	15 (13, 16)

Notes

a ERR = $\alpha_s (D + \beta D^2) (a - e)^{\kappa} a^{\tau}$, as per model B8 (Appendix B), where a = attained age, e = age at exposure, s = sex.

b EAR = $\alpha (D + \beta D^2) (a - e)^{\kappa} a^{\tau}$, as per model B9 (Appendix B), where a = attained age, e = age at exposure.

c CI = Bayesian confidence interval.

TABLE 4.5 Absolute excess risk expressed as risk of exposure-induced cancer incidence (REIC) per 100 people (males and females) exposed to 0.1 Sv. Risk estimates (expressed as a mean with 95% CI [a] for each risk measure) for solid cancer incidence by sex for the current UK population, using generalised ERR and generalised EAR models

Risk estimates are calculated for a population in equilibrium (underlying mortality rates and population structure of the current UK population) from various models fitted to Life Span Study incidence data (Preston et al, 2007). Risks are given as percentages and are assumed to result from an acute uniform whole-body dose of 0.1 Sv

Model	Sex	Oesophagus	Stomach	Colon	Liver	Lung	Non-melanoma skin	Female breast [b]	Bladder	Brain and CNS	Thyroid	All other solid	All solid cancers
ERR	Males	0.38 (−0.10, 4.12)	0.02 (0.00, 0.06)	0.26 (−0.01, 1.31)	0.02 (−0.01, 0.05)	0.24 (0.05, 0.55)	0.15 (−0.35, 0.99)	–	0.40 (0.10, 0.86)	0.15 (−0.01, 5.56)	0.02 (0.00, 0.05)	0.07 (−0.20, 0.44)	1.71
	Females	0.01 (−0.05, 0.07)	0.03 (0.00, 0.05)	0.07 (0.00, 0.28)	0.00 (0.00, 0.01)	0.52 (0.12, 1.16)	0.19 (−0.49, 1.07)	1.05 (0.55, 1.68)	0.09 (0.00, 0.45)	0.11 (−0.01, 4.57)	0.04 (0.01, 0.11)	0.06 (−0.20, 0.32)	2.17
	Both	0.20 (−0.07, 2.08)	0.03 (0.00, 0.05)	0.17 (−0.01, 0.80)	0.01 (0.00, 0.03)	0.38 (0.10, 0.81)	0.17 (−0.40, 0.98)	1.05 (0.55, 1.68)	0.25 (0.05, 0.56)	0.13 (−0.01, 5.06)	0.03 (0.01, 0.07)	0.06 (−0.20, 0.36)	1.96 [c]
EAR	Males	0.06 (−0.05, 0.45)	0.17 (0.01, 0.42)	0.14 (0.00, 0.32)	0.13 (−0.09, 0.39)	0.13 (0.02, 0.28)	0.01 (−0.02, 0.05)	–	0.26 (0.06, 0.55)	0.03 (0.01, 0.06)	0.04 (0.01, 0.09)	0.07 (−0.03, 0.22)	1.04
	Females	0.07 (−0.05, 0.53)	0.22 (0.01, 0.47)	0.07 (0.00, 0.17)	0.01 (0.00, 0.09)	0.22 (0.05, 0.40)	0.01 (−0.03, 0.05)	0.32 (0.20, 0.46)	0.04 (0.00, 0.18)	0.03 (0.01, 0.06)	0.12 (0.04, 0.20)	0.13 (−0.07, 0.33)	1.24
	Both	0.07 (−0.05, 0.49)	0.20 (0.01, 0.41)	0.10 (0.00, 0.23)	0.07 (−0.04, 0.21)	0.17 (0.04, 0.32)	0.01 (−0.02, 0.04)	0.32 (0.20, 0.46)	0.15 (0.03, 0.31)	0.03 (0.01, 0.06)	0.08 (0.03, 0.14)	0.10 (−0.05, 0.26)	1.14 [c]

Notes

a CI = Bayesian confidence interval.

b Risk calculated for female population only.

c Risk sum includes 0.5 x breast cancer risk.

TABLE 4.6 Comparison of risk estimates for mortality due to solid cancers derived in this report with those from various other studies

Source	Population	Test dose, D_t (Sv)	Excess cancer mortality (% Sv^{-1})	Radiation-induced cancer mortality (% Sv^{-1})	Years of life lost (Sv^{-1})	Years of life lost if radiation-induced cancer death occurs (YLLRIC)
Present report	UK	0.1	4.5 (2.2, 7.1) [a,b]	5.4 (2.7, 8.5) [a,b]	–	14 (13, 16) [a,b]
		0.1	3.7 (1.6, 6.1) [c,b]	4.5 (1.9, 7.3) [c,b]	–	15 (13, 16) [c,b]
UNSCEAR, 2008	UK	0.01	4.29 [a,d], 3.64 [c,d]	5.15 [a,d], 4.40 [c,d]	0.71 [a,d], 0.63 [c,d]	13.8 [a,d], 14.4 [c,d]
		0.1	4.38 [a,d], 3.76 [c,d]	5.26 [a,d], 4.54 [c,d]	0.73 [a,d], 0.65 [c,d]	13.8 [a,d], 14.4 [c,d]
		1.0	5.16 [a,d], 4.80 [c,d]	6.21 [a,d], 5.81 [c,d]	0.88 [a,d], 0.85 [c,d]	14.1 [a,d], 14.7 [c,d]
Little et al, 2000 [a]	UK	0.001	10.18 (7.99, 12.65) [b]	12.10 (9.46, 15.05) [b]	1.53 (1.20, 1.91) [b]	12.6 (12.2, 13.0) [b]
		1.0	8.67 (7.06, 10.36) [b]	10.36 (8.41, 12.42) [b]	1.38 (1.11, 1.68) [b]	13.3 (12.8, 13.9) [b]
BEIR V Committee, 1990	USA	0.1	6.95 (5.45, 9.34) [e]	–	–	–
BEIR VII Committee, 2006	USA	0.1	–	7.4 (3.7, 15.0) [b,f]	–	–
ICRP, 1991	UK	1.0	–	8.95 [g], 12.07 [h]	–	–
UNSCEAR, 1994	Japan	0.2	–	12.0 [i], 8.0 [j]	1.34 [i], 1.09 [j]	11.2 [i], 13.6 [j]
		1.0	–	10.9 [i], 7.5 [j]	1.26 [i], 1.00 [j]	11.6 [i], 13.3 [j]
UNSCEAR, 2000	Japan	1.0	7.6 [k,l], 4.9 [k,m]	11.2 [l], 7.4 [m]	1.05 [k,l], 0.79 [k,m]	11.1 [k,l], 12.8 [k,m]
	USA	1.0	–	12.5 [l,a], 9.9 [l,c], 9.3 [m,a], 6.5 [m,c]	–	–
	UK	1.0	–	14.4 [l,a], 12.6 [l,c], 10.1 [m,a], 7.9 [m,c]	–	–
Little et al, 1997a	UK	0.001	–	6.93, 13.79 [n]	1.04, 1.71 [n]	12.4, 15.0 [n]
Little et al, 1997b	European Union/USA	1.0	–	9.29	–	–

Notes

a Generalised ERR model, with multiplicative transport of risk, as described in UNSCEAR (2008), Table 59.
b 95% CI.
c Generalised EAR model with additive transport of risk, as described in UNSCEAR (2008), Table 59.
d Model with linear–quadratic dose response, fitted to full dose range in Preston et al (2004).
e 90% CI.
f Combined 95% subjective uncertainty interval based on weighted EAR and ERR model, taking account of the DDREF.
g NIH projection model.
h Multiplicative projection model.
i Constant relative risk.
j Constant relative risk for first 45 years after exposure, risk declining to zero at attained age 90.
k Males only.
l Model with ERR declining as an exponential function of age at exposure, as described in UNSCEAR (2000), Annex I, Section IV.B.1.
m Model with ERR declining as an exponential function of attained age, as described in UNSCEAR (2000), Annex I, Section IV.B.1.
n Range of risks for models with: (i) power adjustment to ERR for age and time since exposure, (ii) exponential adjustment to ERR for age, (iii) exponential adjustment to ERR for age at exposure, and for years since exposure for those with age at exposure <15, and (iv) exponential adjustment to ERR for age at exposure.

4.4 Uncertainties in Risk Estimates

There are three main sources of uncertainty in the calculation of the risk estimates in this chapter. The first concerns the method of transfer of risks from the Japanese Life Span Study population to the UK population. This is especially important for those cancers, such as cancers of the breast, lung and stomach, where there is a large difference between the underlying cancer rates in the two populations (see Chapter 2, pp 19–20, for further details). In general, it is unclear whether the relative increase in risk or the absolute increase in risk is more stable across populations.

The second source of uncertainty concerns the means by which findings from the Life Span Study are used to infer risks from low doses, possibly received over a protracted period. The Life Span Study doses were generally larger than those received by members of the public for whom the test calculations in this chapter are provided. Furthermore, these doses were received acutely rather than chronically. In order to estimate the risk at low doses or dose rates, a dose and dose rate effectiveness factor (DDREF) is sometimes applied to the risk per unit dose which would be predicted on the basis of linear extrapolation. UNSCEAR, in its 2000 report, reviewed the criteria for setting upper limits of low dose and low dose rate for assessing risks of cancer induction in humans. The criteria suggest that a low dose could be taken to be about 200 mGy and a low dose rate to be about 0.1 mGy per minute (UNSCEAR, 2000, page 79). The value adopted for this reduction factor differs between various organisations. The ICRP in Publication 60 (ICRP, 1991) adopted a DDREF of 2 and retained the same value in its 2007 recommendations (ICRP, 2007). In contrast, the US BEIR VII Committee proposed a reduction factor of 1.5 (BEIR VII Committee, 2006). However, it should be noted that the models fitted in this report generally incorporate a linear–quadratic dose response. As such, application of a DDREF should not be necessary to estimate low dose risks. See Appendix B for a detailed discussion of modelling issues.

The third source of uncertainty concerns the lack of knowledge about the parameters of the risk models derived from the Life Span Study data, as a consequence of uncertainties in the dose estimates. Measurement error on the doses can substantially alter the shape of the dose–response relationship and hence the derived population risk estimates (Thomas et al, 1993). Jablon (1971) investigated the errors in the dosimetry for the Japanese atomic bomb survivors and found that the errors were most likely to be log-normally distributed, with a geometric standard deviation (GSD) of about 30%. The analyses of this report involve adjustment for these dose measurement errors, using a ‘central’ estimate of 35% for GSD.

4.5 Estimates of Radiation Risk for Specific Exposure Examples

Most of the radiation exposure to the general population is from medical exposures or background radiation. The radiation doses received annually from these exposures and hence the cancer risks are generally much lower than (one-tenth or one-hundredth of) the dose of 0.1 Sv considered in Tables 4.3 and 4.4 above. Here we use the age-specific UK-specific estimates for exposure-induced cancer incidence presented in Section 4.3 to estimate the risk of exposure-induced cancer incidence for several types of medical diagnostic and screening examinations.

To conduct the calculations for these examples, we estimated organ-specific radiation doses for the exposure of interest and multiplied these doses by the estimated lifetime risk of exposure-induced cancer

for each organ, for the relevant age at exposure and sex. A table detailing typical organ doses for the example procedures of coronary artery calcification CT, CT colonography and lung CT screening considered below is given in Appendix D (a single summary dose measure, the effective dose, is also provided here for each of these). The total risk was then calculated by summing across all the exposed organs. Although this report is focused on solid cancer risks, in these examples we have also included risks from leukaemia based on models from the Life Span Study (AGIR, 2003).

The simplest example is mammography screening as this exposes only the breast to a measurable radiation dose. A typical two-view screen results in an average dose of 4.5 mSv. Using the EAR model, described in Appendix A, the lifetime risk of radiation-induced breast cancer following exposure per sievert at age 60–64 years is 0.006 or 6 incident breast cancers per 1000 (Table 4.2). Hence, the estimated lifetime risk of radiation-induced breast cancer from mammography screening at age 60 is 6 x 0.0045 = 0.03 per 1000 females screened (Table 4.7). In other words, if 100,000 females aged 60–64 underwent a two-view mammography screen and were followed-up for the rest of their lifetime, these calculations suggest that 3 of these women would develop breast cancer as a result of the radiation exposure from the screening.

4.5.1 Mammography screening for breast cancer

In the UK NHS breast screening programme women aged 50–69 years are currently invited for mammography screening every three years. By 2012 this will be extended to include women aged 47–73 years (NHS Cancer Reform Strategy, 2007). The absorbed glandular breast dose from a two-view screen (which is the current standard screening practice in the UK) is estimated to be approximately 4.5 mSv (Dance et al, 1999; Young et al, 2005). We estimate that the risk of radiation-induced breast cancer incidence following a single two-view screen every three years from age 47–73 years is 0.60 per 1000 under the ERR model or 0.28 under the EAR model (Table 4.7).

If younger pre-menopausal women are to be screened then it is likely that they will need to be screened annually for screening to be effective (Moss et al, 2006). The estimated lifetime risk of radiation-induced breast cancer from annual screening at ages 40–47 is 1.10 per 1000 under the ERR model or 0.61 per 1000 under the EAR model (Table 4.7).

In order to compare the potential radiation risks directly with the benefits from mammography screening it is necessary to estimate the number of cancer deaths from the estimated radiation-induced cancer incidence results described above. Approximate numbers of radiation-induced breast cancer deaths can be estimated by multiplying the incidence estimates in Table 4.7 below by 0.35, since 65% of women with breast cancer are long-term (20 years) survivors so 35% will die of the disease (Cancer Research UK, 2008). Thus the number of deaths among women having annual screening between 40 and 47 years of age is estimated to be 0.4 per 1000 (0.35 x 1.10) based on the ERR model. For screening every three years between 47 and 73 years of age the corresponding number is 0.2 per 1000. The absolute number of breast cancer deaths prevented over a lifetime from regular mammography screening is estimated to be about 1 per 1000 women screened regularly from age 40–47 years and 5 per 1000 women screened regularly from age 47–73 years (Berrington de González and Reeves, 2005; Moss et al, 2006). Hence, for

screening age 47–73 years the net benefit (deaths prevented minus deaths induced) is 4.8 per 1000 (5.0 − 0.2) screened, whereas for screening age 40–47 years it is 0.6 per 1000 (1.0 − 0.4) women screened. These calculations are for females in the general population and cannot be applied directly to females with a higher than average risk of developing breast cancer, such as BRCA mutation carriers.

TABLE 4.7 Risk estimates for breast cancer incidence (exposure-induced cancer incidence, REIC, per 1000 individuals) for females in the current UK population, following mammography screening, using the Preston et al (2002) ERR model and generalised EAR model (Table 4.2)

Risk estimates are calculated from an ERR model fitted to breast cancer incidence data from Massachusetts TB studies (Preston et al, 2002) and from an EAR model fitted to the Life Span Study incidence data (Preston et al, 2007). Breast dose per mammogram = 4.5 mSv

	Age at exposure (years)						
Model	35–39	40–44	50–54	60–64	70–74	Annual 40–47	Every 3 years for 47–73
ERR	0.18	0.15	0.10	0.06	0.03	1.10	0.60
EAR	0.12	0.09	0.05	0.03	0.01	0.61	0.28

4.5.2 Coronary artery calcification CT for screening for ischaemic heart disease

Coronary artery calcification screening with computed tomography has been proposed as a tool for screening for ischaemic heart disease in asymptomatic individuals (Naghavi et al, 2006). It is not currently routinely used for this purpose in the UK. We estimated organ-specific radiation doses for coronary artery calcification CT screening using a protocol from the *ad hoc* International Consortium on Standardization in Cardiac CT (Kim et al, 2009). The effective dose per screen was 2 mSv (Appendix D).

TABLE 4.8 Risk estimates for total cancer incidence (exposure-induced cancer incidence, REIC, per 1000 individuals) by sex in the current UK population, following coronary artery calcification CT screening, using generalised ERR and generalised EAR models (Tables 4.1 and 4.2)

Risk estimates are calculated from various models fitted to Life Span Study incidence data (Preston et al, 2007) and from an ERR model fitted to breast cancer incidence data from Massachusetts TB studies (Preston et al, 2002). Effective dose per CT scan = 2 mSv

		Age at exposure (years)						
Model	Sex	45–49	50–54	55–59	60–64	65–69	70–74	Every 5 years 45–70 males 55–70 females
ERR	Males	0.20	0.23	0.24	0.25	0.24	0.20	1.36
	Females	0.67	0.66	0.66	0.63	0.58	0.44	2.30
EAR	Males	0.11	0.10	0.10	0.09	0.08	0.07	0.55
	Females	0.27	0.24	0.21	0.18	0.15	0.12	0.66

The estimated risk of radiation-induced cancer from a single coronary artery calcification CT screen at age 50–54 years is 0.23 per 1000 under the ERR model or 0.10 per 1000 under the EAR model for males and 0.66 per 1000 under the ERR model or 0.24 per 1000 under the EAR model for females (Table 4.8). The estimated risk from screening every five years for males age 45–70 years is 1.36 per 1000 under the ERR model or 0.55 per 1000 under the EAR model and from age 55–70 years for females is 2.30 per 1000 under the ERR model or 0.66 per 1000 under the EAR model.

4.5.3 CT colonography screening for colorectal cancer

Computed tomography colonography is being evaluated as a method for colorectal cancer screening (Johnson et al, 2008). We used the protocol from a recent US screening trial (Berrington de González et al, 2010) to estimate typical organ doses from a CT colonography screen (Appendix D). The effective dose per screen was estimated to be 8 mSv.

The estimated lifetime risk of radiation-induced cancer from a single screen at age 50–54 years is 0.64 per 1000 under the ERR model or 0.71 per 1000 under the EAR model for males and 0.43 per 1000 under the ERR model or 0.48 per 1000 under the EAR model for females (Table 4.9). For repeated screens every five years between age 50 and 70 years the estimated risk is 2.63 per 1000 under the ERR model or 2.91 per 1000 under the EAR model for males and 1.97 per 1000 under the ERR model or 1.94 per 1000 under the EAR model for females.

TABLE 4.9 Risk estimates for total cancer incidence (exposure-induced cancer incidence, REIC, per 1000 individuals) by sex in the current UK population, following CT colonography screening, using generalised ERR and generalised EAR models (Tables 4.1 and 4.2)

Effective dose per CT scan = 8 mSv

		Age at exposure (years)						
Model	**Sex**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**Every 5 years 50–70**
ERR	Males	0.68	0.64	0.60	0.54	0.47	0.38	2.63
	Females	0.43	0.43	0.43	0.42	0.39	0.31	1.97
EAR	Males	0.79	0.71	0.63	0.55	0.45	0.36	2.71
	Females	0.51	0.48	0.44	0.39	0.34	0.28	1.94

4.5.4 Lung CT screening for lung cancer

Lung CT is being evaluated as a screening method for lung cancer in smokers in several large randomised trials. We estimated the organ-specific radiation doses from a single lung CT screen using the protocol from the US National Lung Screening Trial (Berrington de González et al, 2008). The mean effective dose was 1 mSv per screen (see Appendix D for a breakdown of the doses according to the organ irradiated).

The estimated lifetime risk of radiation-induced cancer from a single screen at age 50–54 years is 0.14 per 1000 under the ERR model or 0.08 per 1000 under the EAR model for males, and 0.40 per 1000 under the ERR model or 0.17 per 1000 under the EAR model for females (Table 4.10). For annual screening from age 50–70 years the estimated risk is 3.01 per 1000 under the ERR model or 1.41 per 1000 under the EAR model for males, and 7.95 per 1000 under the ERR model or 2.88 per 1000 under the EAR model for females. The risk estimates are higher for females because of the additional risk of radiation-induced breast cancer and a higher risk of radiation-induced lung cancer.

These estimates should be regarded with some caution in view of the uncertainty about the combined effects of smoking and radiation on lung cancer risk described in Chapter 3, page 123. Thus, while the values quoted above may be appropriate for non-smokers, they may underestimate the radiation risks to smokers.

TABLE 4.10 Risk estimates for total cancer incidence (exposure-induced cancer incidence, REIC, per 1000 individuals) by sex in the current UK population, following lung CT screening, using generalised ERR and generalised EAR models (Tables 4.1 and 4.2)

Risk estimates are calculated from various models fitted to Life Span Study incidence data (Preston et al, 2007) and from an ERR model fitted to breast cancer incidence data from Massachusetts TB studies (Preston et al, 2002). Effective dose per CT scan = 1 mSv

		Age at exposure (years)						
Model	Sex	45–49	50–54	55–59	60–64	65–69	70–74	Annual screening 50–70
ERR	Males	0.11	0.14	0.15	0.15	0.14	0.12	3.01
	Females	0.40	0.40	0.40	0.38	0.35	0.27	7.95
EAR	Males	0.08	0.08	0.07	0.07	0.06	0.05	1.41
	Females	0.19	0.17	0.15	0.13	0.11	0.09	2.88

4.5.5 Summary

Diagnostic and screening medical radiation exposures are one of the most common sources of radiation exposure to the general population, after natural background exposures (Watson et al, 2005). Doses from most of these exposures are very small (0.1–10 mSv effective dose) and hence cancer risks are also likely to be small. The examples here highlight the higher risks for younger ages at exposure (see, for example, the estimates for mammography screening, Table 4.7) as well as the higher risks for females for examinations that involve exposure to the breast tissue (eg coronary artery calcification CT screening, Table 4.8). Table 4.11 summaries the risks, both individually and combined, from these examinations when they are repeated as part of a screening programme. The benefits, where established, should outweigh the small risk of radiation-induced cancer (eg post-menopausal mammography screening). However, the benefits from coronary artery calcification CT, CT colonography and lung CT screening have not yet been clearly established and so even small risks may outweigh the benefits, particularly for

younger ages at exposure because radiation risks are higher whilst the absolute benefits are likely to be lower. Results from randomised screening trials, such as the US National Lung Screening Trial and European NELSON trial, will provide important information about the benefits from lung CT screening that can be compared to these estimates of radiation risks.

TABLE 4.11 Lifetime risk estimates for total cancer incidence (exposure-induced cancer incidence, REIC, per 1000 individuals) by sex in the current UK population, following repeated screening examinations, using generalised ERR and generalised EAR models (Tables 4.1 and 4.2)

Risk estimates are calculated from various models fitted to Life Span Study incidence data (Preston et al, 2007) and from an ERR model fitted to breast cancer incidence data from Massachusetts TB studies (Preston et al, 2002)

		Screening test, frequency and age at exposure (years)				
Model	Sex	Mammography Every 3 years Age 47–73	Coronary artery calcification CT Every 5 years Age 45–70 males Age 55–70 females	CT colonography Every 5 years Age 55–70	Lung CT Every year Age 50–70	Total risk from all screening tests
ERR	Males	n.a.	1.36	2.63	3.01	7.00
	Females	0.60	2.30	1.97	7.95	12.82
EAR	Males	n.a.	0.55	2.71	1.41	4.67
	Females	0.28	0.66	1.94	2.88	5.76

4.6 Conclusions

Estimates for the UK population of the lifetime risk of radiation-induced solid cancers have been developed here. These estimates are based on risk models used by UNSCEAR (2008) as well as related models. For mortality from all solid cancers combined, the lifetime risk estimated here is less than that in previous evaluations, mainly because – with longer follow-up from Life Span Study – the risk projected to arise several decades after exposure is lower than before. Additionally, a new dosimetry system has been implemented for the Life Span Study since the previous estimates were derived. This had the effect of reducing the overall solid cancer risk per unit of radiation dose by around 8% compared to the previous dosimetry system. Risk estimates have also been affected by some changes in the method used to transfer the radiation risks from the Japanese population to the UK population.

The risks of radiation-induced cancer calculated in this report are consistent with others calculated internationally. The estimates here can be considered as refinements to those previously available, based on more recent and informative data. While the risk of cancer from ionising radiation from medical imaging is individually small, collectively it can produce a potential hazard.

5 Summary and Conclusions

The aims of the Subgroup on Solid Cancer Risk of the Advisory Group on Ionising Radiation were two-fold:

> to review information on the risk of solid cancers, such as breast and prostate cancer but not cancers such as lymphoma or leukaemia, from exposure to ionising radiation,
>
> to derive risk estimates applicable to the UK population with a quantitative assessment of the effects of typical radiation exposures the public may experience.

The population is exposed to different kinds of radiations, which are classified according to the effects they produce on matter and living material. Ionising radiation arises from natural and man-made radioactive materials and includes cosmic rays, X-rays, neutrons and the radiations emitted from radioactive materials including alpha and beta particles and gamma rays. An atom becomes ionised if sufficient energy interacts with it to cause one of its electrons to be ejected. The ionisation of atoms in a cell can cause damage to the molecules that regulate vital cell functions.

The effect of ionising radiation on the human body depends upon a number of factors including:

a the radiation dose,

b whether the exposure is from an external source or from intakes of radioactive materials,

c the distribution of exposure in the body and the time period over which it is received,

d the sensitivity of the individual exposed, which can be influenced by both sex and age.

There is a considerable amount of information on the risks of solid cancer from various epidemiological studies of radiation-exposed populations. However, the amount of information from these studies varies considerably, because of differences in, *inter alia*,

a statistical precision, which in itself is influenced by factors such as the numbers of cases or deaths available for study,

b potential for bias (systematic error), which may arise, for example, through the manner in which the study population was identified and in which the cancers or deaths were ascertained,

c availability and reliability of individual estimates of radiation dose,

d scope of the study, eg whether it covers only low doses or only high doses, only childhood exposures or only adult exposures, and low or high linear energy transfer (LET) radiations.

Overall, the Life Span Study of Japanese atomic bomb survivors is the most informative study on the risks of radiation-induced solid cancers. Some studies of medical, occupational and environmental exposures are also informative when considering specific cancers and/or specific types of exposure (eg protracted exposures or high LET radiations).

For many solid cancers, there is epidemiological evidence of an association with exposure to ionising radiation and in most instances this association is judged to be causal – specifically for cancers of the oesophagus, stomach, colon, rectum, liver, lung, bone, non-melanoma skin, breast (female), bladder, thyroid, and brain and other central nervous system tumours. For cancers of the salivary glands and ovary, the association is probably causal.

There is some uncertainty – particularly for less common cancers where data are more sparse – about how radiation risks vary with factors such as sex, age at exposure and time since exposure. Also, information for specific cancers on risks from protracted and low doses is limited, owing to low statistical power.

It is unclear whether cancers of the pancreas, connective tissue, melanoma of skin, uterine cervix, body of uterus, prostate, testis and kidney can be induced by ionising radiation. In general, the data for these cancers are too sparse, but the possibility of a small raised risk cannot be ruled out.

In addition, whilst there is good evidence on the effects of alpha radiation on inducing some cancers such as lung, liver and bone, based on studies of exposures from radon and plutonium, for other cancers the epidemiological data are insufficient to provide direct estimates of risks from this kind of radiation. The risks from radon exposure and the implications for public health were considered in more detail in an earlier report by the Advisory Group on Ionising Radiation (AGIR, 2009a).

Estimates of the lifetime risk of radiation-induced solid cancers have been developed in this report. These estimates are based on risk models used by UNSCEAR (2008) as well as related models. For mortality from all solid cancers combined, the lifetime risk estimated here is less than that in previous evaluations, mainly because – with longer follow-up from the Life Span Study – the risk projected to arise several decades after exposure is lower than before. Additionally, a new dosimetry system has been implemented for the Life Span Study since the previous estimates were derived. This had the effect of reducing the overall solid cancer risk per unit of radiation dose by around 8% compared to the previous dosimetry system. Risk estimates have also been affected by some changes in the method used to transfer the radiation risks from the Japanese population to the UK population.

As an illustration of their application, these risk models have been used to estimate the total cancer risk associated with several medical procedures. A summary is shown in Table 5.1 and more details are given in Chapter 4.

The risks of radiation-induced cancer calculated in this report are consistent with others produced internationally. The estimates here can be considered as refinements based on more recent and informative data, to estimates previously available from other reports by bodies such as UNSCEAR. While the risk of cancer from ionising radiation from medical imaging is individually small, collectively it can produce an important potential hazard (see, for example, risk estimates for current levels of CT scan use in the USA – Berrington de González et al, 2009). This is particularly so when these examinations are performed in the context of screening in the general population where the background cancer risks are much lower than for those people who are tested as symptomatic patients in a clinical situation (see Table 4.11).

TABLE 5.1 Summary of the range* of estimates of the total lifetime risk of cancer induced by various diagnostic screening scenarios

Risks are expressed as the number of cancer cases expected in 1000 people undergoing the specified screening protocol

Medical imaging investigation	Screening protocol	Lifetime risk of a radiation-induced cancer (expressed as number of cancer cases per 1000 people)
Mammography	Every 3 years 47–73 year olds	0.3–0.6 (breast cancer risk for women only)
Coronary artery calcification CT	Every 5 years 45–70 year old males 55–70 year old females	 Males 0.6–1.4 Females 0.7–2.3
CT colonography	Every 5 years 50–70 year olds, both sexes	Males 2.6–2.7 Females 1.9–2.0
Lung CT	Every year 50–70 year olds, both sexes	Males 1.4–3.0 Females 2.9–8.0
All screening tests listed above	All protocols listed above	Males 4.7–7.0 Females 5.8–12.8

* The range relates to the two methods used here to estimates lifetime risks. For CT colonography, the two methods give essentially the same result for males.

Subgroups of the population have a higher risk of cancer from radiation exposure. Chapter 4 draws attention to the higher risks associated with exposures at younger ages (eg mammography screening) and the higher risks for women than men with examinations that involve exposure to the breast tissue (eg coronary artery calcification CT screening).

The benefits, where established, should outweigh the small risk of radiation-induced cancer (eg for post-menopausal mammography screening) in symptomatic patients being investigated for a suspected medical disorder. However, this may not be the case in people without symptoms. The benefits from coronary artery calcification CT, CT colonography and lung CT screening have not yet been clearly established. Consequently, even small risks may outweigh the benefits, particularly for younger ages at exposure because radiation risks are higher whilst the absolute benefits are likely to be lower. Results from randomised screening trials, such as the US National Lung Screening Trial and European NELSON trial, will provide important information about the benefits from lung CT screening that can be compared to these estimates of radiation risks.

The use of ionising radiation in medical screening of individuals and populations has increased in recent years and raises legitimate concerns. The AGIR notes the interest shown in individual screening by the UK government Committee on Medical Aspects of Radiation in the Environment in its twelfth report (COMARE, 2007). The AGIR, and the HPA in general, will continue to work with relevant professional bodies and regulators to determine risk–benefit ratios of medical procedures involving radiation exposure, including screening of the general population, so that the implications of their use are understood and they are used appropriately.

6 References

Abramson DH and Frank CM (1998). Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. *Ophthalmology,* **105,** 573–80.

AGIR (1999a). Guidelines on Patient Dose to Promote the Optimisation of Protection for Diagnostic Medical Exposures. Report of an Advisory Group on Ionising Radiation. *Doc NRPB*, **10**(1), 1–43.

AGIR (1999b). Genetic Heterogeneity in the Population and its Implications for Radiation Risk. Report of an Advisory Group on Ionising Radiation. *Doc NRPB*, **10**(3), 1–47.

AGIR (2000). Risks of Second Cancer in Therapeutically Irradiated Populations: Comparison with Cancer Risks in the Japanese Atomic Bomb Survivors and in Other Exposed Groups. Report of an Advisory Group on Ionising Radiation. *Doc NRPB*, **11**(1), 1–105.

AGIR (2003). Risk of Leukaemia and Related Malignancies following Radiation Exposure: Estimates for the UK Population. Report of the independent Advisory Group on Ionising Radiation. *Doc NRPB,* **14**(1), 1–119. Available at www.hpa.org.uk

AGIR (2007). Review of Risks from Tritium. Report of the independent Advisory Group on Ionising Radiation. *Doc HPA,* RCE-4, 1–90. Available at www.hpa.org.uk

AGIR (2009a). Radon and Public Health in the United Kingdom. Report of the independent Advisory Group on Ionising Radiation. *Doc HPA*, RCE-11, 1–240. Available at www.hpa.org.uk

AGIR (2009b). High Dose Radiation Effects and Tissue Injury. Report of the independent Advisory Group on Ionising Radiation. *Doc HPA*, RCE-10, 1–94. Available at www.hpa.org.uk

AGIR (2010). Circulatory Disease Risk. Report of the independent Advisory Group on Ionising Radiation. *Doc HPA*, RCE-16, 1–116. Available at www.hpa.org.uk

AGNIR (2002). Health Effects from Ultraviolet Radiation. Report of an Advisory Group on Non-ionising Radiation. *Doc NRPB,* **13**(1), 1–282. Available at www.hpa.org.uk

Andersson M, Carstensen B and Storm HH (1995). Mortality and cancer incidence after cerebral arteriography with or without Thorotrast. *Radiat Res,* **142,** 305–20.

Aoyama T, Yamamoto Y, Kato H, et al (1998). Mortality survey of Japanese radiological technologists during the period 1969–1993. *Radiat Prot Dosim,* **77,** 123–8.

Armstrong B (1990). The effects of measurement errors on relative risk regressions. *Am J Epidemiol,* **132,** 1176–84.

Artalejo FR, Lara SC, Manzano BA, et al (1997). Occupational exposure to ionising radiation and mortality among workers of the former Spanish Nuclear Energy Board. *Occup Environ Med,* **54**(3), 202–8.

Ashmore JP, Krewski D, Zielinski JM, Jiang H, Semenciw R and Band PR (1998). First analysis of mortality and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol,* **148,** 564–74.

Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV, Garber V, et al (1998). Chernobyl-related thyroid cancer in children in Belarus: a case–control study. *Radiat Res,* **150,** 349–56.

Atkinson WD, Law, DV, Bromley KJ and Inskip HM (2004). Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–97. *Occup Environ Med,* **61,** 577–85.

Atkinson WD, Law DV and Bromley KJ (2007). A decline in mortality from prostate cancer in the UK Atomic Energy Authority workforce. *J Radiol Prot,* **27,** 437–45.

Auvinen A, Pukkala E, Hyvonen H, Hakama M and Rytomaa T (2002). Cancer incidence among Finnish nuclear reactor workers. *J Occup Environ Med,* **44,** 634–8.

Auvinen A, Salonen L, Pekkanen J, Pukkala E, Ilus T and Kurttio P (2005). Radon and other natural radionuclides in drinking water and risk of stomach cancer: a case–cohort study in Finland. *Int J Cancer,* **114,** 109–13.

Bauer S, Gusev BI, Pivina LM, Apsalikov KN and Grosche B (2005). Radiation exposure due to local fallout from Soviet atmospheric nuclear weapons testing in Kazakhstan: solid cancer mortality in the Semipalatinsk historical cohort, 1960–1999. *Radiat Res,* **164,** 409–19.

Baverstock KF and Papworth DG (1989). The UK radium luminiser survey. In *Risks from Radium and Thorotrast* (DM Taylor et al, eds). BIR Report 21, pp72–6. London, British Institute of Radiology.

Baverstock KF, Papworth D and Vennart J (1981). Risks of radiation at low dose rates. *Lancet,* **I,** 430–33.

Baxter NN, Tepper JE, Durham SB, Rothenberger DA and Virnig BA (2005). Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology,* **128,** 819–24.

Becker N, Liebermann D, Wesch H and van Kaick G (2008). Mortality among Thorotrast-exposed patients and an unexposed comparison group in the German Thorotrast study. *Eur J Cancer,* **44,** 1259–68.

BEIR III Committee (1980). Committee on Biological Effects of Ionizing Radiation. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR IV Committee (1988). Committee on Biological Effects of Ionizing Radiation. Health Risks of Radon and Other Internally Deposited Alpha-emitters. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR V Committee (1990) Committee on Biological Effects of Ionizing Radiation. Health Effects of Exposure to Low Levels of Ionizing Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR VI Committee (1999). Committee on Health Risks of Exposure to Radon. Health Effects of Exposure to Radon. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR VII Committee (2006). Committee to Assess Health Risks from Exposure to Low Levels of Ionising Radiation. Health Risks from Exposure to Low Levels of Ionising Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

Bennett J, Little MP and Richardson S (2004). Flexible dose–response models for Japanese atomic bomb survivor data: Bayesian estimation and prediction of cancer risk. *Radiat Environ Biophys,* **43,** 233–45.

Beral V, Fraser P, Carpenter L, Booth M, Brown A and Rose G (1988). Mortality of employees of the Atomic Weapons Establishment, 1951–82. *Br Med J,* **297,** 757–70.

Berrington de González A and Reeves GK (2005). Mammographic screening before age 50 years in the UK: comparison of the radiation risks with the mortality benefits. *Br J Cancer,* **93,** 590–96.

Berrington de González A, Kim KP and Berg C (2008). Lung CT screening before age 55: radiation risks compared to potential benefits. *J Med Screen,* **15,** 153–8.

Berrington de González A, Mahesh M, Kim KP, Bhargavan M, Lewis R, Mettler F and Land C (2009). Projected cancer risks from computed tomographic scans performed in the United States in 2007. *Arch Intern Med,* **169**(22), 2071–7.

Berrington de González A, Kim KP and Yee J (2010). CT colonography: perforation rates and potential radiation risks. *Gastrointest Endosc Clin N Am,* **20**(2), 279–91.

Berwick M (2006). Soft tissue sarcomas. In *Cancer Epidemiology and Prevention,* Third Edition (D Schottenfeld and JF Fraumeni, eds). New York, Oxford University Press, pp959–74.

Bhatia S, Robison LL, Oberlin O, Greenberg M, Bunin G, Fossati-Bellani F and Meadows AT (1996). Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med,* **334,** 745–51.

Birchall A and James AC (1994). Uncertainty analysis of the effective dose per unit exposure from radon progeny and implications for ICRP risk-weighting factors. *Radiat Prot Dosim,* **53,** 133–40.

Bithell JF and Stewart AM (1975). Prenatal irradiation and childhood malignancy: a review of British data from the Oxford survey. *Br J Cancer,* **31,** 271–7.

Boffetta P, Mannetje A, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, et al (2005). Occupational X-ray examinations and lung cancer risk. *Int J Cancer,* **115,** 263–7.

Boice JD Jr (1997). Radiation epidemiology: past and present. In *Implications of New Data on Radiation Cancer Risk* (JD Boice Jr, ed). NCRP Proceedings No. 18, pp7–28.

Boice JD Jr, Day NE, Andersen A, Brinton LA, Brown R, Choi NW, et al (1985). Second cancers following radiation treatment for cervical cancer: an international collaboration among cancer registries. *J Natl Cancer Inst,* **74,** 955–75.

Boice JD Jr, Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, et al (1987). Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst,* **79,** 1295–311.

Boice JD Jr, Engholm G, Kleinerman RA, Blettner M, Stovall M, Lisco H, et al (1988). Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res,* **116,** 3–55.

Boice JD Jr, Blettner M, Kleinerman RA, Engholm G, Stovall M, Lisco H, et al (1989). Radiation dose and breast cancer risk in patients treated for cancer of the cervix. *Int J Cancer,* **44,** 7–16.

Boice JD Jr, Preston D, Davis FG and Monson RR (1991). Frequent chest X-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat Res,* **125**(2), 214–22.

Boice JD Jr, Harvey EB, Blettner M, Stovall M and Flannery JT (1992). Cancer in the contralateral breast after radiotherapy for breast cancer. *N Engl J Med,* **326,** 781–85.

Boice JD, Cohen SS, Mumma MT, Dupree Ellis E, Eckerman KF, Leggett RW, et al (2006). Mortality among radiation workers at Rocketdyne (Atomics International), 1948–1999. *Radiat Res,* **166,** 98–115.

Brenner DJ, Curtis RE, Hall EJ and Ron E (2000). Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer,* **88,** 398–406.

Brenner DJ, Little JB and Sachs RK (2001). The bystander effect in radiation oncogenesis: II. A quantitative model. *Radiat Res,* **155,** 402–8.

Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, et al (2003). Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *Proc Natl Acad Sci USA,* **100,** 13761–6.

Breslow NE and Day NE (1980). Statistical Methods in Cancer Research. Volume I: *The Analysis of Case–Control Studies.* Lyon, International Agency for Research on Cancer.

Breslow NE and Day NE (1987). Statistical Methods in Cancer Research. Volume II: *The Design and Analysis of Cohort Studies.* Lyon, International Agency for Research on Cancer.

Brinkley D and Haybittle JL (1969). The late effects of artificial menopause by X-radiation. *Br J Radiol,* **42,** 519–21.

Brown SC, Schonbeck MF, McClure D, Baron AE, Navidi WC, Byers T and Ruttenber AJ (2004). Lung cancer and internal lung doses among plutonium workers at the Rocky Flats Plant: a case–control study. *Am J Epidemiol,* **160,** 163–72.

Cagnon CH, Cody DD, McNitt-Gray MF, Seibert JA, Judy PF and Aberle DR (2006). Description and implementation of a quality control program in an imaging-based clinical trial. *Acad Radiol,* **13**(11), 1431–41.

Cancer Research UK (2008). Statistics on the most commonly diagnosed types of cancer in the UK. Available at http://info.cancerresearchuk.org/cancerstats/types/

Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, et al (1995). Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res,* **142,** 117–32.

Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, et al (2005a). Risk of thyroid cancer after exposure to ^{131}I in childhood. *J Natl Cancer Inst,* **97,** 724–32.

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al (2005b). Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Br Med J,* **331,** 77–80.

Cardis E, Howe G, Ron E, Bebeshko V, Bogdanova T, Bouville A, et al (2006). Cancer consequences of the Chernobyl accident: 20 years after. *J Radiol Prot,* **26,** 127–40.

Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: estimates of radiation-related cancer risks. *Radiat Res,* **167,** 396–416.

Carnes BA, Grahn D and Hoel D (2003). Mortality of atomic bomb survivors predicted from laboratory animals. *Radiat Res,* **160,** 159–67.

Carpenter L, Higgins C, Douglas A, Fraser P, Beral V and Smith P (1994). Combined analysis of mortality in three United Kingdom nuclear industry workforces, 1946–1988. *Radiat Res,* **138,** 224–38.

Carpenter LM, Higgins CD, Douglas AJ, Maconochie NE, Omar RZ, Fraser P, Beral V and Smith PG (1998). Cancer mortality in relation to monitoring for radionuclide exposure in three UK nuclear industry workforces. *Br J Cancer,* **78,** 1224–32.

Carr ZA, Kleinerman RA, Stovall M, Weinstock RM, Griem ML and Land CE (2002). Malignant neoplasms after radiation therapy for peptic ulcer. *Radiat Res,* **157,** 668–77.

CERRIE (2004). Report of the Committee Examining Radiation Risks of Internal Emitters (CERRIE). Chilton, NRPB. Available at www.cerrie.org.

Chang-Claude J, Becher H, Blettner M, Qiu SL, Yang GR and Wahrendorf J (1997). Familial aggregation of oesophageal cancer in a high incidence area in China. *Int J Epidemiol,* **26,** 1159–65.

Checkoway H, Heyer NJ and Demers PA (1996). An updated mortality follow-up study of Florida phosphate industry workers. *Am J Ind Med,* **30,** 452–60.

Chrouser K, Leibovich B, Bergstralh E, Zincke H and Blute M (2005). Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. *J Urol,* **174**(1), 107–11.

Cohen BL (1997). Problems in the radon vs lung cancer test of the linear no-threshold theory and a procedure for resolving them. *Health Phys,* **72,** 623–8.

Cologne JB, Tokuoka S, Beebe GW, Fukuhara T and Mabuchi K (1999). Effects of radiation on incidence of primary liver cancer among atomic bomb survivors. *Radiat Res,* **152,** 364–73.

Correa P and Chen VW (1994). Gastric cancer. In *Cancer Surveys.* Trends in Cancer Incidence and Mortality, Volumes 19/20, pp55–76 (R Doll et al, eds). Cold Spring Harbor Laboratory Press, Imperial Cancer Research Fund.

Daley T and Darling M (2003). Nonsquamous cell malignant tumours of the oral cavity: an overview. *J Can Dent Assoc,* **69,** 577–82.

Damber L, Johansson L, Johansson R and Larsson LG (2002). Thyroid cancer after X-ray treatment of benign disorders of the cervical spine in adults. *Acta Oncol,* **41,** 25–8.

Dance DR, Skinner CL, Young KC, Beckett JR and Kotre CJ (2000). Additional factors for the estimation of mean glandular breast dose in the UK mammography dosimetry protocol. *Phys Med Biol,* **45**(11), 3225–40.

Darby SC, Reeves G, Key T, Doll R and Stovall M (1994). Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. *Int J Cancer,* **56,** 793–801.

Darby SC, Whitley E, Howe GR, Hutchings SJ, Kusiak RA, Lubin JH, et al (1995). Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J Natl Cancer Inst,* **87,** 378–84.

Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al (2005a). Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case–control studies. *Br Med J,* **330,** 223–6.

Darby SC, McGale P, Taylor CW and Peto R (2005b). Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300 000 women in US SEER cancer registries. *Lancet Oncol,* **6,** 557–65.

Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al (2006). Residential radon and lung cancer – detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health,* **32**(Suppl 1), 1–83.

Daugaard S (2004). Current soft-tissue sarcoma classifications. *Eur J Cancer,* **40,** 543–8.

Davis FG, Boice JD Jr, Hrubec Z and Monson RR (1989). Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. *Cancer Res,* **49,** 6130–36.

Davis S, Stepanenko V, Rivkind N, Kopecky KJ, Voillequé P, Shakhtarin V, et al (2004a). Risk of thyroid cancer in the Bryansk Oblast of the Russian Federation after the Chernobyl power station accident. *Radiat Res,* 162, 241–48.

Davis S, Kopecky KJ, Hamilton TE and Onstad L (2004b). Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine-131 from the Hanford nuclear site. *J Am Med Assoc,* **292,** 2600–13.

DeGroot LJ, Reilly M, Pinnameneni K and Refetoff S (1983). Retrospective and prospective study of radiation-induced thyroid disease. *Am J Med,* **74,** 852–62.

Delongchamp RR, Mabuchi K, Yoshimoto Y and Preston DL (1997). Cancer mortality among atomic bomb survivors exposed *in utero* or as young children, October 1950 – May 1992. *Radiat Res,* **147,** 385–95.

de Vathaire F, Shamsadin A, Grimaud E, et al (1995). Solid malignant neoplasms after childhood cancer irradiation: decrease of the relative risk with time after irradiation. *CR Acad Sci Ser Gen Vie Sci,* **318,** 483–90.

de Vathaire F, Schlumberger M, Delisle MJ, Francese C, Challeton C, de la Genardiére E, et al (1997). Leukaemias and cancers following iodine-131 administration for thyroid cancer. *Br J Cancer,* **75,** 734–9.

de Vathaire F, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, et al (1999a). Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br J Cancer,* **79,** 1884–93.

de Vathaire F, Hardiman C, Shamsaldin A, Campbell S, Grimaud E, Hawkins M, et al (1999b). Thyroid carcinomas after irradiation for a first cancer during childhood. *Arch Intern Med,* **159,** 2713–19.

Dickman PW, Holm LE, Lundell G, Boice JD Jr and Hall P (2003). Thyroid cancer risk after thyroid examination with I131: a population-based cohort study in Sweden. *Int J Cancer,* **106,** 580–87.

Dickson RJ (1969). The late results of radium treatment for benign uterine hemorrhage. *Br J Radiol,* **42,** 582–94.

Donaldson SS and Hancock SL (1996). Second cancers after Hodgkin's disease in childhood (editorial). *N Engl J Med,* **334,** 792–4.

Doniachi I (1963). Effects including carcinogenesis of iodine-131 and X rays on the thyroid of experimental animals – a review. *Health Phys,* **9,** 1357–62.

Dondon MG, de Vathaire F, Shamsaldin A, Doyon F, Diallo I, Ligot L, et al (2004). Cancer mortality after radiotherapy for a skin hemangioma during childhood. *Radiother Oncol,* **72,** 87–93.

Doody MM, Lonstein JE, Stovall M, Hacker DG, Luckyanov N and Land CE (2000). Breast cancer mortality after diagnostic radiography: findings from the US Scoliosis Cohort Study. *Spine,* **25,** 2052–63.

Doody MM, Freedman DM, Alexander BH, Hauptmann M, Miller JS, Rao RS, et al (2006). Breast cancer incidence in US radiologic technologists. *Cancer,* **106,** 2707–15.

dos Santos Silva I, Jones M, Malveiro F and Swerdlow A (1999). Mortality in the Portuguese Thorotrast study. *Radiat Res,* **152,** (6 Suppl), S88–S92.

dos Santos Silva I, Malveiro F, Jones ME and Swerdlow AJ (2003). Mortality after radiological investigation with radioactive Thorotrast: a follow-up study of up to fifty years in Portugal. *Radiat Res,* **159,** 521–34.

Dottorini ME, Lomuscio G, Mazzucchelli L, Vignati A and Colombo L (1995). Assessment of female fertility and carcinogenesis after iodine-131 therapy for differentiated thyroid carcinoma. *J Nucl Med,* **36,** 21–7.

Edmonds CJ and Smith T (1986). The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br J Radiol,* **59**(697), 45–51.

Engels H, Swaen GM, Slangen J, van Amersvoort L, Holmstock L, Van Mieghem E, et al (2005). Radiation exposure and cause specific mortality among nuclear workers in Belgium (1969–1994). *Radiat Prot Dosim,* **117,** 373–81.

EPA (Environmental Protection Agency) (2003). EPA Assessment of Risks from Radon in Homes. EPA 402-R-03-003. Washington DC, US Environmental Protection Agency.

Ewertz M, Machado SG, Boice JD Jr and Jensen OM (1984). Endometrial cancer following treatment for breast cancer: a case–control study in Denmark. *Br J Cancer,* **50,** 687–92.

Ferlay J, Bray F, Pisani P, et al (2001). GLOBOCAN 2000: Cancer Incidence, Mortality and Prevalence Worldwide. Version 1 (CD-ROM). IARC Cancer Base No. 5. Lyon, International Agency for Research on Cancer.

Fletcher O, Easton D, Anderson K, Gilham C, Jay M and Peto J (2004). Lifetime risks of common cancers among retinoblastoma survivors. *J Natl Cancer Inst,* **96,** 357–63.

Flint-Richter P and Sadetzki S (2007). Genetic predisposition for the development of radiation-associated meningioma: an epidemiological study. *Lancet Oncol,* **8,** 403–10.

Forman D and Burley VJ (2006). Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Practice Res Clin Gastroenterol,* **20,** 633–49.

Franceschi S, Fassina A, Talamini R, Mazzolini A, Vianello S, Bidoli E, et al (1989). Risk factors for thyroid cancer in northern Italy. *Int J Epidemiol,* **18**(3), 578–84.

Franceschi S, Talamini A, Fassina A and Bidoli E (1990). Diet and epithelial cancer of the thyroid gland. *Tumori,* **76,** 331–8.

Franceschi S, Preston-Martin S, Dal Maso L, Negri E, La Vecchia C, Mack WJ, et al (1999). A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control,* **10**(6), 583–95.

Franklin J, Pluetschow A, Paus M, Specht L, Anselmo AP, Aviles A, et al (2006). Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials. *Ann Oncol,* **17,** 1749–60.

Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J and Boyle P (1999). Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet,* **353,** 2111–15.

Fraser P, Carpenter L, Maconochie N, Higgins C, Booth M and Beral V (1993). Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946–86. *Br J Cancer,* **67,** 615–24.

Freedman DM, Sigurdson A, Rao RS, Hauptmann M, Alexander B, Mohan A, et al (2003). Risk of melanoma among radiologic technologists in the United States. *Int J Cancer,* **103,** 556–62.

Frome EL, Cragle DL and McLain RW (1990). Poisson regression analysis of the mortality among a cohort of World War II nuclear industry workers. *Radiat Res,* **123,** 138–52.

Frome EL, Cragle DL, Watkins JP, Wing S, Shy CM, Tankersley WG and West CM (1997). A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. *Radiat Res,* **148,** 64–80.

Fujiwara S, Kusumi S, Cologne J, Akahoshi M, Kodama K and Yoshizawa H (2000). Prevalence of anti-hepatitis C virus antibody and chronic liver disease among atomic bomb survivors. *Radiat Res,* **154,** 12–19.

Fujiwara S, Sharp GB, Cologne JB, Kusumi S, Akahoshi M, Kodama K, Suzuki G and Yoshizawa H (2003). Prevalence of hepatitis B virus infection among atomic bomb survivors. *Radiat Res,* **159,** 780–86.

Galanti MR, Ekbom A, Grimelius L and Yuen J (1997). Parental cancer and risk of papillary and follicular thyroid carcinoma. *Br J Cancer,* **75**(3), 451–6.

Gilbert ES (1984). Some effects of random dose measurement errors on analyses of atomic bomb survivor data. *Radiat Res,* **98,** 591–605.

Gilbert ES, Cragle DL and Wiggs LD (1993). Updated analyses of combined mortality data for workers at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Weapons Plant. *Radiat Res,* **136,** 408–21.

Gilbert ES, Koshurnikova NA, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, et al (2000). Liver cancers in Mayak workers. *Radiat Res,* **154,** 246–52.

Gilbert ES, Stovall M, Gospodarowicz M, Van Leeuwen FE, Andersson M, Glimelius B, et al (2003). Lung cancer after treatment for Hodgkin's disease: focus on radiation effects. *Radiat Res,* **159,** 161–73.

Gilbert ES, Koshurnikova NA, Sokolnikov ME, Shilnikova NS, Preston DL, Ron E, et al (2004). Lung cancer in Mayak workers. *Radiat Res,* **162,** 505–16.

Godley P and Kim SW (2002). Renal cell carcinoma. Genitourinary system. *Curr Opin Oncol*, **14,** 280–85.

Greenland S and Robins J (1994). Invited commentary: ecologic studies – biases, misconceptions, and counter-examples. *Am J Epidemiol,* **139,** 747–60.

Griem ML, Kleinerman RA, Boice JD Jr, Stovall M, Shefner D and Lubin JH (1994). Cancer following radiotherapy for peptic ulcer. *J Natl Cancer Inst,* **86**(11), 842–9.

Grosche B, Kreuzer M, Kreisheimer M, Schnelzer M and Tschense A (2006). Lung cancer risk among German male uranium miners: a cohort study, 1946–1998. *Br J Cancer,* **95,** 1280–87.

Gudbjartsson T, Jónasdóttir TJ, Thoroddsen A, Einarsson GV, Jónsdóttir GM, Kristjánsson K, et al (2002). A population-based familial aggregation analysis indicates genetic contribution in a majority of renal cell carcinomas. *Int J Cancer,* **100,** 476–9.

Guérin S, Dupuy A, Anderson H, Shamsaldin A, Svahn-Tapper G, Moller T, et al (2003). Radiation dose as a risk factor for malignant melanoma following childhood cancer. *Eur J Cancer,* **39,** 2379–86.

Guérin S, Guibout C, Shamsaldin A, Dondon MG, Diallo I, Hawkins M, et al (2007). Concomitant chemo-radiotherapy and local dose of radiation as risk factors for second malignant neoplasms after solid cancer in childhood: a case–control study. *Int J Cancer,* **120,** 96–102.

Guibout C, Adjadj E, Rubino C, Shamsaldin A, Grimaud E, Hawkins M, et al (2005). Malignant breast tumors after radiotherapy for a first cancer during childhood. *J Clin Oncol,* **23,** 197–204.

Hall P, Holm LE, Lundell G, Bjelkengren G, Larsson LG, Lindberg S, et al (1991). Cancer risks in thyroid cancer patients. *Br J Cancer,* **64,** 159–63.

Hall P, Berg G, Bjelkengren G, Boice JD Jr, Ericsson UB, Hallquist A, et al (1992). Cancer mortality after iodine-131 therapy for hyperthyroidism. *Int J Cancer,* **50,** 886–90.

Hall P, Mattsson A and Boice JD Jr (1996). Thyroid cancer after diagnostic administration of iodine-131. *Radiat Res,* **145,** 86–92.

Hamilton TE, Van Belle G and LoGerfo JP (1987). Thyroid neoplasia in Marshall Islanders exposed to nuclear fallout. *J Am Med Assoc,* **258,** 629–36.

Hamilton PM, Chiacchierini RP and Kaczmarek R (1989). Follow-up of Persons who had Iodine-131 and Other Diagnostic Procedures during Childhood and Adolescence. FDA Publication 89-8276. Rockville MD, CDRH, Food and Drug Administration.

Hancock SL, Cox RS and McDougall R (1991). Thyroid diseases after treatment of Hodgkin's disease. *N Engl J Med,* **325,** 599–605.

Hancock SL, Tucker MA and Hoppe RT (1993). Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst,* **85,** 25–31.

Hanford JM, Quimby EH and Frantz VK (1962). Cancer arising many years after radiation therapy. Incidence after irradiation of benign lesions in the neck. *J Am Med Assoc,* **181,** 404–10.

Hankey BF, Silverman DT and Kaplan R (1993). Urinary bladder. In *SEER Cancer Statistics Review, 1973–1990* (BA Miller et al, eds). NIH Publication No. 93-2789, ppxxvi.1–xxvi.17.

Hawkins MM, Wilson LM, Burton HS, Potok MH, Winter DL, Marsden HB and Stovall MA (1996). Radiotherapy, alkylating agents, and risk of bone cancer after childhood cancer. *J Natl Cancer Inst,* **88,** 270–78.

Hemminki K and Li X (2004). Age-specific familial risks for renal cell carcinoma with evidence on recessive heritable effects. *Kidney Int,* **65,** 2298–302.

Henrichs K, Bogner L, Nekolla E, et al (1995). Extended dosimetry for studies with Ra-224 patients. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium* (G Van Kaick et al, eds), pp33–38. Singapore, World Scientific.

Hildreth NG, Shore RE, Hempelmann LH and Rosenstein M (1985). Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. *Radiat Res,* **102,** 378–91.

Hildreth NG, Shore RE and Dvoretsky PM (1989). The risk of breast cancer after irradiation of the thymus in infancy. *N Engl J Med,* **321,** 1281–4.

Hill DA, Gilbert E, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al (2005). Breast cancer risk following radiotherapy for Hodgkin lymphoma: modification by other risk factors. *Blood,* **106,** 3358–65.

Hodgson JT and Jones RD (1990). Mortality of a cohort of tin miners 1941–86. *Br J Ind Med,* **47,** 665–76.

Holm L-E, Wiklund KE, Lundell GE, Bergman NA, Bjelkengren G, Cederquist ES, et al (1988). Thyroid cancer after diagnostic dose of iodine-131: a retrospective cohort study. *J Natl Cancer Inst,* **80,** 1132–8.

Holm LE, Wiklund KE, Lundell GE, Bergman NA, Bjelkengren G, Ericsson UB, et al (1989). Cancer risk in population examined with diagnostic doses of ^{131}I. *J Natl Cancer Inst,* **81,** 302–6.

Holm LE, Hall P, Wiklund K, Lundell G, Berg G, Bjelkengren G, et al (1991). Cancer risk after iodine-131 therapy for hyperthyroidism. *J Natl Cancer Inst,* **83,** 1072–7.

Hopke PK, Jensen BL, Li C-S, Montassier N, Wasiolek P, Cavallo A, Gatsby K, Socolow RH and James AC (1995). Assessment of the exposure to and dose from radon decay products in normally occupied homes. *Environ Sci Tech,* **29,**1359–64.

Hornung RW and Meinhardt TJ (1987). Quantitative risk assessment of lung cancer in US uranium miners. *Health Phys,* **52**(4), 417–30.

Hornung RW, Deddens JA and Roscoe RJ (1998). Modifiers of lung cancer risk in uranium miners from the Colorado Plateau. *Health Phys,* **74,** 12–21.

Horn-Ross PL, Ljung BM and Morrow M (1997). Environmental factors and the risk of salivary gland cancer. *Epidemiology,* **8**(4), 414–19.

Howe GR (1995). Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the atomic bomb survivors study. *Radiat Res,* **142**, 295–304.

Howe GR and McLaughlin J (1996). Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res,* **145,** 694–707.

Howe GR and Stager RH (1996). Lung cancer mortality after exposure to radon decay products in Beaverlodge cohort based on revised exposure estimates. *Radiat Res,* **146,** 37–42.

Howe GR, Nair RC, Newcombe HB, Miller AB and Abbatt JD (1986). Lung cancer mortality (1950–1980) in relation to radon daughter exposure in a cohort of workers at the Eldorado Beaverlodge uranium mine. *J Natl Cancer Inst,* **77**(2), 357–62.

Howe GR, Nair RC, Newcombe HB, Miller AB, Burch JD and Abbatt JD (1987). Lung cancer mortality (1950–1980) in relation to radon daughter exposure in a cohort of workers at the Port Radium uranium mine: possible modification of risk by exposure rate. *J Natl Cancer Inst,* **79**(6), 357–62.

Howe GR, Zablotska LB, Fix JJ, Egel J and Buchanan J (2004). Analysis of the mortality experience amongst US nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat Res,* **162,** 517–26.

Huang J, Walker R, Groome PG, Shelley W and Mackillop WJ (2001). Risk of thyroid carcinoma in a female population after radiotherapy for breast carcinoma. *Cancer,* **92,** 1411–18.

Hughes JS, Watson SJ, Jones AL, et al (2005). Review of the radiation exposure of the UK population. *J Radiol Prot,* **25,** 493–6.

Hunter N, Muirhead CR and Zhang W (2006). Possible selection effects for radiation risk estimates in Japanese A-bomb survivors: reanalysis of acute radiation symptoms data. *Radiat Environ Biophys,* **45**(1), 17–26.

Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F and Woodward M (2005). Type II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer,* **92,** 2076–83.

IARC (1988). *Alcohol Drinking.* IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 44. Lyon, International Agency for Research on Cancer. Available at http://monographs.iarc.fr

ICRP (1991). 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. *Ann ICRP*, **21**(1–3).

ICRP (1993). Protection against Radon-222 at Home and at Work. ICRP Publication 65. *Ann ICRP*, **23**(2).

ICRP (1998). Genetic Susceptibility to Cancer. ICRP Publication 79. *Ann ICRP*, **28**(1/2).

ICRP (2005). Low-dose Extrapolation of Radiation-related Cancer Risk. ICRP Publication 99. *Ann ICRP*, **34**(4).

ICRP (2007). 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. *Ann ICRP*, **37**(2–3).

Inskip PD, Monson RR, Wagoner JK, Stovall M, Davis FG, Kleinerman RA and Boice JD Jr (1990). Cancer mortality following radium treatment for uterine bleeding. *Radiat Res,* **123,** 331–44.

Inskip PD, Stovall M and Flannery JT (1994). Lung cancer risk and radiation dose among women treated for breast cancer. *J Natl Cancer Inst,* **86,** 983–8.

Inskip PD, Ekbom A, Galanti MR, Grimelius L and Boice JD Jr (1995). Medical diagnostic X rays and thyroid cancer. *J Natl Cancer Inst,* **87,** 1613–21.

Ishikawa Y, Mori T, Kato Y, Machinami R, Priest ND and Kitagawa T (1993). Systemic deposits of thorium in Thorotrast patients with particular reference to sites of minor storage. *Radiat Res,* **135,** 244–8.

Ivanov VK, Tsyb AF, Petrov AV, Maksioutov MA, Shilyaeva TP and Kochergina EV (2002). Thyroid cancer incidence among liquidators of the Chernobyl accident. Absence of dependence of radiation risks on external radiation dose. *Radiat Environ Biophys,* **41,** 195–8.

Ivanov VK, Gorski AI, Tsyb AF, Ivanov SI, Naumenko RN and Ivanova LV (2004). Solid cancer incidence among the Chernobyl emergency workers residing in Russia: estimation of radiation risks. *Radiat Environ Biophys,* **43,** 35–42.

Ivanov VK, Gorski AI, Kashcheev VV, Maksioutov MA and Tumanov KA (2009). Latent period in induction of radiogenic solid tumors in the cohort of emergency workers. *Radiat Environ Biophys,* **48,** 247–52.

Iwasaki T, Murata M, Ohshima S, Miyake T, Kudo S, Inoue Y, et al (2003). Second analysis of mortality of nuclear industry workers in Japan, 1986–1997. *Radiat Res,* **159,** 228–38.

Jablon S (1971). Atomic Bomb Radiation Dose Estimation at ABCC. ABCC TR/23-71. Hiroshima, Atomic Bomb Casuality Commission.

Jacob P, Bogdanova TI, Buglova E, Chepurniy M, Demidchik Y, Gavrilin Y, Kenigsberg J, Meckbach R, Schotola C, Shinkarev S, Tronko MD, Ulanovsky A, Vavilov S and Walsh L (2006). Thyroid cancer risk in areas of Ukraine and Belarus affected by the Chernobyl accident. *Radiat Res,* **165,** 1–8.

Jenkinson HC, Winter DL, Marsden HB, Stovall MA, Stevens MC, Stiller CA and Hawkins MM (2007). A study of soft tissue sarcomas after childhood cancer in Britain. *Br J Cancer,* **97,** 695–9.

Jones AL, Oatway WB, Hughes JS and Simmonds JR (2007). Review of trends in the UK population dose. *J Radiol Prot,* **27**(4), 381–90.

Johnson CD, Chen MH, Toledano AY, Heiken JP, Dachman A, Kuo MD, et al (2008). Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med,* **359**(12), 1207–17. Erratum in *N Engl J Med,* **359**(26), 2853.

Kaldor JM, Day NE, Bell J, Clarke EA, Langmark F, Karjalainen S, et al (1992). Lung cancer following Hodgkin's disease: a case–control study. *Int J Cancer,* **52,** 677–81.

Kaldor JM, Day NE, Kittelmann B, Pettersson F, Langmark F, Pedersen D, et al (1995). Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case–control study. *Int J Cancer,* **63,** 1–6.

Kanno J, Onodera H, Furuta K, Maekawa A, Kasuga T and Hayashi Y (1992). Tumor-promoting effects of both iodine deficiency and iodine excess in the rat thyroid. *Toxicol Pathol,* **20,** 226–35.

Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE and Wallgren A (1998a). Intracranial tumors after exposure to ionizing radiation during infancy. A pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. *Radiat Res,* **150,** 357–64.

Karlsson P, Holmberg E, Samuelsson A, Johansson KA and Wallgren A (1998b). Soft tissue sacoma after treatment for breast cancer – a Swedish population-based study. *Eur J Cancer,* **34,** 2068–75.

Kazakov VS, Demidchik EP and Astakhova LN (1992). Thyroid cancer after Chernobyl. *Nature,* **359,** 21.

Kellerer AM and Rossi HH (1978). A generalized formulation of dual radiation action. *Radiat Res,* **75,** 471–88.

Kendall GM and Smith TJ (2002). Doses to organs and tissues from radon and its decay products. *J Radiol Prot,* **22,** 389–406.

Kendall GM, Muirhead CR, MacGibbon BH, O'Hagan JA, Conquest AJ, Goodill AA, et al (1992). Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *Br Med J,* **304,** 220–25.

Khursheed A, Hillier MC, Shrimpton PC and Wall BF (2002). Influence of patient age on normalized effective doses calculated for CT examinations. *Br J Radiol,* **75,** 819–30.

Kim K-P, Einstein A and Berrington de González A (2009). Coronary artery calcification screening: radiation dose and cancer risk. *Arch Int Med,* **169,** 1188–94.

Kleinerman RA, Boice JD Jr, Storm HH, Sparen P, Andersen A, Pukkala E, et al (1995). Second primary cancer after treatment for cervical cancer. *Cancer,* **76,** 442–52.

Kleinerman RA, Stovall M, Tarone RE and Tucker MA (2004). Radiotherapy and genetic susceptibility to cancer in a cohort of retinoblastoma patients. *Ann Epidemiol,* **14,** 593.

Kleinerman RA, Stovall M, Tarone RE and Tucker MA (2005a). Gene environment interactions in a cohort of irradiated retinoblastoma patients. *Radiat Res,* **163**(6), 701–2.

Kleinerman RA, Tucker MA, Tarone RE, Abramson DH, Seddon JM, Stovall M, et al (2005b). Risk of new cancers following radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol,* **23,** 2272–9.

Knox EG, Stewart AM, Kneale GW and Gilman EA (1987). Prenatal irradiation and childhood cancer. *J Radiol Prot,* **7,** 177–89.

Kono S and Hirohata T (1996). Nutrition and stomach cancer. *Cancer Causes Control,* **7,** 41–55.

Kopecky KJ, Davis S, Hamilton TE, Saporito MS and Onstad LE (2004). Estimation of thyroid radiation doses for the Hanford thyroid disease study: results and implications for statistical power of the epidemiological analyses. *Health Phys,* **87,** 15–32.

Kopecky KJ, Stepanenko V, Rivkind N, Voilleque P, Onstad L, Shakhtarin V, et al (2006). Childhood thyroid cancer, radiation dose from Chernobyl, and dose uncertainties in Bryansk Oblast, Russia: a population-based case–control study. *Radiat Res,* **166,** 367–74.

Koshurnikova NA, Gilbert ES, Sokolnikov M, Khokhryakov VF, Miller S, Preston DL, Romanov SA, Shilnikova NS, Suslova KG and Vostrotin VV (2000). Bone cancers in Mayak workers. *Radiat Res,* **154,** 237–45.

Koshurnikova NA, Gilbert ES, Shilnikova NS, Sokolnikov M, Preston DL, Kreisheimer M, et al (2002). Studies on the Mayak nuclear workers: health effects. *Radiat Environ Biophys,* **41,** 29–31.

Kossenko MM, Thomas TL, Akleyev AV, Krestinina LY, Startsev NV, Vyushkova OV, et al (2005). The Techa River cohort: study design and follow-up methods. *Radiat Res,* **164,** 591–601.

Kreisheimer M, Koshurnikova NA, Nekolla E, Khokhryakov VF, Romanow SA, Sokolnikov ME, et al (2000). Lung cancer mortality among male nuclear workers of the Mayak facilities in the former Soviet Union. *Radiat Res,* **154,** 3–11.

Krestinina LY, Preston DL, Ostroumova EV, Degteva MO, Ron E, Vyushkova OV, et al (2005). Protracted radiation exposure and cancer mortality in the Techa River cohort. *Radiat Res,* **164,** 602–11.

Kreuzer M, Walsh L, Schnelzer M, Tschense A and Grosche B (2008). Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960–2003. *Br J Cancer,* **99,** 1946–53.

Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al (2005). Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology,* **16,** 137–45.

Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al (2006). A combined analysis of North American case–control studies of residential radon and lung cancer. *J Toxicol Environ Health A,* **69,** 533–97.

Kurttio P, Salonen L, Ilus T, Pekkanen J, Pukkala E and Auvinen A (2006). Well water radioactivity and risk of cancers of the urinary organs. *Environ Res,* **102,** 333–8.

Kusiak RA, Springer J, Ritchie AC, and Muller J (1991). Carcinoma of the lung in Ontario gold miners: possible aetiological factors. *Br J Ind Med,* **48,** 808–17.

Lagarde F and Pershagen G (1999). Parallel analyses of individual and ecologic data on residential radon, cofactors, and lung cancer in Sweden. *Am J Epidemiol,* **149,** 268–74.

Land CE, Saku T, Hayashi Y, Takahara O, Matsuura H, Tokuoka S, et al (1996). Incidence of salivary gland tumors among atomic bomb survivors, 1950–1987. Evaluation of radiation-related risk. *Radiat Res,* **146,** 28–36.

Land CE, Tokunaga M, Koyama K, Soda M, Preston DL, Nishimori I and Tokuoka S (2003). Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950–1990. *Radiat Res,* **160,** 707–17.

Langner I, Blettner M, Gundestrup M, Storm H, Aspholm R, Auvinen A, et al (2004). Cosmic radiation and cancer mortality among airline pilots: results from a European cohort study (ESCAPE). *Radiat Environ Biophys,* **42,** 247–56.

Laurier D, Tirmarche M, Mitton N, Valenty M, Richard P, Poveda S, et al (2004). An update of cancer mortality among the French cohort of uranium miners: extended follow-up and new sources of data for causes of death. *Eur J Epidemiol,* **19**(2), 139–46.

Leuraud K, Billon S, Bergot D, Tirmarche M, Caer S, Quesne B and Laurier D (2007). Lung cancer risk associated to exposure to radon and smoking in a case–control study of French uranium miners. *Health Phys,* **92,** 371–8.

Lichter MD, Karagas MR, Mott LA, Spencer SK, Stukel TA and Greenberg ER (2000). Therapeutic ionizing radiation and the incidence of basal cell carcinoma and squamous cell carcinoma. The New Hampshire Skin Cancer Study Group. *Arch Dermatol,* **136,** 1007–11.

Lili W, Lin L, Quanfu S, et al (1994). A cohort study of cancer mortality on workers exposed to thorium-containing dust in Baotou Iron and Steel Company. *Chin J Radiol Med Prot,* **14,** 93–6.

Lindberg S, Karlsson P, Arvidsson B, Holmberg E, Lunberg LM and Wallgren A (1995). Cancer incidence after radiotherapy for skin haemangioma during infancy. *Acta Oncol,* **34,** 735–40.

Linos E, Raine T, Alonso A and Michaud D (2007). Atopy and risk of brain tumors: a meta-analysis. *J Natl Cancer Inst,* **99,** 1544–50.

Little J (1999). *Epidemiology of Childhood Cancer.* IARC Scientific Publication No. 149. Lyon, International Agency for Research on Cancer.

Little MP (1993). Risks of radiation-induced cancer at high doses and dose rates. *J Radiol Prot,* **13,** 3–25.

Little MP (2002a). Absence of evidence for differences in the dose-response for cancer and non-cancer endpoints by acute injury status in the Japanese atomic-bomb survivors. *Int J Radiat Biol,* **178,** 1001–10.

Little MP (2002b). The proportion of thyroid cancers in the Japanese atomic bomb survivors associated with natural background radiation. *J Radiol Prot,* **22,** 279–91.

Little MP (2003). Risks associated with ionizing radiation. *Br Med Bull,* **68,** 259–75.

Little MP and Charles MW (1997). The risk of non-melanoma skin cancer incidence in the Japanese atomic bomb survivors. *Int J Radiat Biol,* **71,** 589–602.

Little MP and Lambert BE (2008). Systematic review of experimental studies on the relative biological effectiveness of tritium. *Radiat Environ Biophys,* **47,** 71–93.

Little MP and Muirhead CR (1996). Evidence for curvilinearity in the cancer incidence dose-response in the Japanese atomic bomb survivors. *Int J Radiat Biol,* **70,** 83–94.

Little MP and Muirhead CR (1998). Curvature in the cancer mortality dose response in Japanese atomic bomb survivors: absence of evidence of threshold. *Int J Radiat Biol,* **74**(4), 471–80.

Little MP and Muirhead CR (2000). Derivation of low-dose extrapolation factors from analysis of curvature in the cancer incidence dose response in Japanese atomic bomb survivors. *Int J Radiat Biol,* **76,** 939–953.

Little MP and Wakeford R (2001). The bystander effect in C3H 10T½ cells and radon-induced lung cancer. *Radiat Res,* **156,** 695–99.

Little MP and Wakeford R (2008). Systematic review of epidemiological studies of exposure to tritium. *J Radiol Prot,* **28,** 9–32.

Little MP, Hawkins MM, Shore RE, Charles MW and Hildreth NG (1991). Time variations in the risk of cancer following irradiation in childhood. *Radiat Res,* **126**(3), 304–16. Erratum in *Radiat Res,* 1992; **132**(1), 126.

Little MP, Hawkins MM, Charles MW and Hildreth NG (1992). Fitting the Armitage-Doll model to radiation-exposed cohorts and implications for population cancer risks. *Radiat Res,* **132,** 207–21.

Little MP, de Vathaire F, Charles MW, Hawkins MM and Muirhead CR (1997a). Variations with time and age in the relative risks of solid cancer incidence after radiation exposure. *J Radiol Prot,* **17,** 159–77.

Little MP, Muirhead CR, Goossens LHJ, Kraan BCP, Cooke RM, Harper FT and Hora SC (1997b). Probabilistic Accident Consequence Uncertainty Analysis. Late Health Effects Uncertainty Assessment. Volume 1. Main Report. NUREG/CR-6555 (EUR 16774).

Little MP, de Vathaire F, Charles MW, Hawkins MM and Muirhead CR (1998a). Variations with time and age in the risks of solid cancer incidence after radiation exposure in childhood. *Stat Med,* **17**(12), 1341–55.

Little MP, de Vathaire F, Shamsaldin A, Oberlin O, Campbell S, Grimaud E, et al (1998b). Risks of brain tumour following treatment for cancer in childhood: modification by genetic factors, radiotherapy and chemotherapy. *Int J Cancer,* **78,** 269–75.

Little MP, Muirhead CR and Charles MW (1999a). Describing time and age variations in the risk of radiation-induced solid tumour incidence in the Japanese atomic bomb survivors using generalized relative and absolute risk models. *Stat Med,* **18,** 17–33.

Little MP, Weiss HA, Boice JD Jr, Darby SC, Day NE and Muirhead CR (1999b). Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. *Radiat Res,* 1**52**(3), 280–92. Erratum in *Radiat Res,* **153**(2), 243 (2000).

Little MP, Deltour I and Richardson S (2000). Projection of cancer risks from the Japanese atomic bomb survivors to the England and Wales population taking into account uncertainty in risk parameters. *Radiat Environ Biophys,* **39,** 241–52.

Little MP, Hall P and Charles MW (2007). Are cancer risks associated with exposures to ionising radiation from internal emitters greater than those in the Japanese A-bomb survivors? *Radiat Environ Biophys,* **46,** 299–310.

Little MP, Hoel DG, Molitor J, Boice JD Jr, Wakeford R and Muirhead CR (2008). New models for evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 report. *Radiat Res,* **169,** 660–76.

Longstreth WT Jr, Phillips LE, Drangsholt M, Koepsell TD, Custer BS, Gehrels JA and van Belle G (2004). Dental X-rays and the risk of intracranial meningioma: a population-based case-control study. *Cancer,* **100,** 1026–34.

Lönn S, Bhatti P, Alexander BH, Pineda MA, Doody MM, Struewing JP and Sigurdson AJ (2007). Papillary thyroid cancer and polymorphic variants in TSHR- and RET-related genes: a nested case–control study within a cohort of US radiologic technologists. *Cancer Epidemiol Biomarkers Prev,* **16,** 174–7.

Lubin JH and Boice JD Jr (1997). Lung cancer risk from residential radon: meta-analysis of eight epidemiologic studies. *J Natl Cancer Inst,* **89,** 49–57.

Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe GR, Kunz E, et al (1995). Lung cancer risk in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst,* **87,** 817–27.

Lubin JH, Schafer DW, Ron E, Stovall M and Carroll RJ (2004a). A reanalysis of thyroid neoplasms in the Israeli tinea capitis study accounting for dose uncertainties. *Radiat Res,* **161,** 359–68.

Lubin JH, Wang ZY, Boice JD Jr, Xu ZY, Blot WJ, De Wang L and Kleinerman RA (2004b). Risk of lung cancer and residential radon in China: pooled results of two studies. *Int J Cancer,* **109,** 132–7.

Lundell M (1994). Estimates of absorbed dose in different organs in children treated with radium for skin hemangiomas. *Radiat Res,* **140,** 327–33.

Lundell M and Holm L-E (1995). Risk of solid tumors after irradiation in infancy. *Acta Oncol,* **34,** 727–34.

Lundell M, Hakulinen T and Holm L-E (1994). Thyroid cancer after radiotherapy for skin hemangioma in infancy. *Radiat Res,* **140,** 334–9.

Lundell M, Mattsson A, Hakulinen T and Holm LE (1996). Breast cancer after radiotherapy for skin hemangioma in infancy. *Radiat Res,* **145,** 225–30.

Lundell M, Mattsson A, Karlsson P, Holmberg E, Gustafsson A and Holm LE (1999). Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants. *Radiat Res,* **151,** 626–32.

Lyon JL, Alder SC, Stone MB, Scholl A, Reading JC, Holubkov R, et al (2006). Thyroid disease associated with exposure to the Nevada nuclear weapons test site radiation: a reevaluation based on corrected dosimetry and examination data. *Epidemiology,* **17,** 604–14.

McCollough CH, Ulzheimer S, Halliburton SS, Shanneik K, White RD and Kalender WA (2007). Coronary artery calcium: a multi-institutional, multimanufacturer international standard for quantification at cardiac CT. *Radiology,* **243,** 527–38.

McCredie M (1994). Bladder and kidney cancers. In *Cancer Surveys*. Trends in Cancer Incidence and Mortality, Volumes 19/20, pp343–68 (R Doll et al, eds). Cold Spring Harbor Laboratory Press, Imperial Cancer Research Fund.

McCullagh P and Nelder JA (1989). *Generalized Linear Models* (Second Edition). London, Chapman and Hall.

McGale P and Darby SC (2005). Low doses of ionizing radiation and circulatory diseases: a systematic review of the published epidemiological evidence. *Radiat Res,* **163,** 247–57.

McGeoghegan D and Binks K (2000a). The mortality and cancer morbidity experience of workers at the Springfields uranium production facility, 1946–95. *J Radiol Prot,* **20**(2), 111–37.

McGeoghegan D and Binks K (2000b). The mortality and cancer morbidity experience of workers at the Capenhurst uranium enrichment facility 1946–95. *J Radiol Prot,* **20**(4), 381–401.

McGeoghegan D and Binks K (2001). The mortality and cancer morbidity experience of employees at the Chapelcross plant of British Nuclear Fuels plc, 1955–95. *J Radiol Prot,* **21**(3), 221–50.

McGeoghegan D, Gillies M, Riddell AE and Binks K (2003). Mortality and cancer morbidity experience of female workers at the British Nuclear Fuels Sellafield Plant, 1946–1998. *Am J Ind Med,* **44**(6), 653–63.

McTiernan A, Weiss N and Daling J (1984). Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. *J Natl Cancer Inst,* **73,** 575–81.

Mack TM (1995). Sarcomas and other malignancies of soft tissue, retroperitoneum, peritoneum, pleura, heart, mediastinum, and spleen. *Cancer,* **75,** 211–44.

Marsh JW and Birchall A (2000). Sensitivity analysis of the weighted equivalent lung dose per unit exposure from radon progeny. *Radiat Prot Dosim,* **87,** 167–78.

Mattsson A, Hall P, Rudén BI and Rutqvist LE (1997). Incidence of primary malignancies other than breast cancer among women treated with radiation therapy for benign breast disease. *Radiat Res,* **148,** 152–60.

Mattsson A, Rudén BI, Hall P, Wilking N and Rutqvist LE (1993). Radiation-induced breast cancer: long-term follow-up of radiation therapy for benign breast disease. *J Natl Cancer Inst,* **85,** 1679–85.

Mattsson A, Rudén BI, Palmgren J and Rutqvist LE (1995). Dose- and time-response for breast cancer risk after radiation therapy for benign breast disease. *Br J Cancer,* **72,** 1054–61.

Maxon HR, Saenger EL, Thomas SR, Buncher CR, Kereiakes JG, Shafer ML and McLaughlin CA (1980). Clinically important radiation-associated thyroid disease. A controlled study. *J Am Med Assoc,* **244,** 1802–5.

Menu-Branthomme A, Rubino C, Shamsaldin A, Hawkins MM, Grimaud E, Dondon MG, et al (2004). Radiation dose, chemotherapy and risk of soft tissue sarcoma after solid tumours during childhood. *Int J Cancer,* **110,** 87–93.

Mettler FA Jr, Thomadsen BR, Bhargavan M, Gilley DB, Gray JE, Lipoti JA, et al (2008). Medical radiation exposure in the US in 2006: preliminary results. *Health Phys,* **95,** 502–7.

Miller RC, Randers-Pehrson G, Geard CR, Hall EJ and Brenner DJ (1999). The oncogenic transforming potential of the passage of single α particles through mammalian cell nuclei. *Proc Natl Acad Sci USA,* **96,** 19–22.

Miller RW, Boice JD and Curtis RE (2006). Bone cancer. In *Cancer Epidemiology and Prevention*, Third Edition, pp946–58 (D Schottenfeld and JF Fraumeni, eds). New York, Oxford University Press.

Minniti G, Traish D, Ashley S, Gonsalves A and Brada M (2005). Risk of second brain tumour after conservative surgery and radiotherapy for pituitary adenoma: update after an additional 10 years. *J Clin Endocrinol Metab,* **90,** 800–804.

Mohan AK, Hauptmann M, Freedman DM, Ron E, Matanoski GM, Lubin JH, et al (2003). Cancer and other causes of mortality among radiologic technologists in the United States. *Int J Cancer,* **103**(2), 259–67.

Morgan WF (2003a). Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects *in vivo*, clastogenic factors and transgenerational effects. *Radiat Res,* **159**(5), 581–96.

Morgan WF (2003b). Non-targeted and delayed effects of exposure to ionizing radiation: I. Radiation-induced genomic instability and bystander effects *in vitro*. *Radiat Res,* **159**(5), 567–80.

Morrison HI, Villeneurve PJ, Lubin JH and Schaubel DE (1998). Radon-progeny exposure and lung cancer risk in a cohort of Newfoundland fluorspar miners. *Radiat Res,* **150,** 58–65.

Moss SM, Cuckle H, Evans A, Johns L, Waller M and Bobrow L; Trial Management Group (2006). Effect of mammography screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet,* **368**(9552), 2053–60.

Monson RR and MacMahon B (1984). Prenatal X-ray exposure and cancer in children. In *Radiation Carcinogenesis: Epidemiology and Biological Significance*, pp97–105 (JD Boice and JF Fraumeni, eds). New York, Raven Press.

Mori T, Kido C, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, et al (1999a). Summary of entire Japanese Thorotrast follow-up study: updated 1998. *Radiat Res,* **152**(6 Suppl), S84–S87.

Mori T, Fukutomi K, Kato Y, Hatakeyama S, Machinami R, Tanooka H, et al (1999b). 1998 results of the first series of follow-up studies on Japanese Thorotrast patients and their relationships to an autopsy series. *Radiat Res,* **152**(6 Suppl), S72–S80.

Muirhead CR, Goodill AA, Haylock RGE, Vokes J, Little MP, Jackson DA, et al (1999). Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. *J Radiol Prot,* **19,** 3–26.

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC and Zhang W (2009). Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer,* **100,** 206–12.

Munoz N and Day NE (1996). Esophageal cancer. In *Cancer Epidemiology and Prevention*, Second Edition, pp681–706 (D Schottenfeld and JF Fraumeni Jr, eds). New York, Oxford University Press.

Murai M and Oya M (2004). Renal cell carcinoma: etiology, incidence and epidemiology. *Curr Opin Urol,* **14,** 229–33.

Naghavi M, Falk E, Hecht HS and Shah PK; SHAPE Task Force (2006). The first SHAPE (Screening for Heart Attack Prevention and Education) guideline. *Crit Pathw Cardiol,* **5**(4), 187–90.

Najarian T and Colton T (1978). Mortality from leukemia and cancer in shipyard nuclear workers. *Lancet,* **I,** 1018–20.

NCI (National Cancer Institute) (1999). Uncertainties in Radiation Dosimetry and their Impact on Dose–response Analyses (E Ron and FO Hoffman, eds). Bethesda MD, National Institutes of Health.

NCRP (National Council on Radiation Protection and Measurements) (1980). The Influence of Dose and its Distribution in Time on Dose–response Relationships for Low-LET Radiations. NCRP Report 64. Bethesda MD, NCRP.

NCRP (National Council on Radiation Protection and Measurements) (1990). The Relative Biological Effectiveness of Radiations of Different Quality. NCRP Report 104. Bethesda MD, NCRP.

Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al (2006). New primary neoplasms of the central nervous system in survivors of childhood cancer. A report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst,* **98,** 1528–37.

Negri E, Dal Maso L, Ron E, La Vecchia C, Mark SD, Preston-Martin S, et al (1999). A pooled analysis of case–control studies of thyroid cancer. II. Menstrual and reproductive factors. *Cancer Causes Control,* **10**(2), 143–55.

Nekolla EA, Kellerer AM, Kuse-Isingschulte M, Eder E and Spiess H (1999). Malignancies in patients treated with high doses of radium-224. *Radiat Res,* **152**(6 Suppl), S3–S7.

Nekolla EA, Kreisheimer M, Kellerer AM, Kuse-Isingschulte M, Gössner W and Spiess H (2000). Induction of malignant bone tumors in radium-224 patients: risk estimates based on the improved dosimetry. *Radiat Res,* **153,** 93–103.

Neugut AI, Ahsan H, Robinson E and Ennis RD (1997). Bladder carcinoma and other second malignancies after radiotherapy for prostate carcinoma. *Cancer,* **79,** 1600–604.

Department of Health (2007). NHS Cancer Reform Strategy. Available at www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081006

Nomura A (1996). Stomach cancer. In *Cancer Epidemiology and Prevention,* Second Edition, pp707–24 (D Schottenfeld and JF Fraumeni Jr, eds). New York, Oxford University Press.

Norat T, Lukanova A, Ferrari P and Riboli E (2002). Meat consumption and colorectal cancer risk: dose–response meta-analysis of epidemiological studies. *Int J Cancer,* **98,** 241–56.

NRPB (1998). *Living with Radiation,* Fifth Edition. Chilton, NRPB.

NRPB (1993). Estimates of Late Radiation Risks to the UK Population. *Doc NRPB*, **4**(4), 15–157.

NRPB (2004). Review of the Scientific Evidence for Limiting Exposure to Electromagnetic Fields (0–300 GHz). *Doc NRPB*, **15**(3),1–215.

ONS (Office for National Statistics) (2004a). Mortality Statistics Cause. Review of the Registrar General on Deaths by Cause, Sex and Age, in England and Wales, 2003. Series DH2 No. 30. London, Stationery Office.

ONS (Office for National Statistics) (2004b). Cancer Statistics Registrations. Registrations of Cancer Diagnosed in 2001, England. Series MB1 No. 32. London, Stationery Office.

ONS (Office for National Statistics) (2006). Cancer Statistics: Registrations. Registrations of Cancer in 2004, England. Series MB1, No. 35. London, ONS.

ONS (Office for National Statistics) (2008). Mortality Statistics, England and Wales. London, ONS.

ONS (Office for National Statistics) (2009). Mortality Statistics: Cause, England and Wales, 2007. Series DH2, London, ONS.

Ohshima M and Ward J (1984). Promotion of N-methyl-N-nitrosourea-induced thyroid tumors by iodine deficiency in F344/NCr rats. *J Natl Cancer Inst,* **73**(1), 289–96.

Ohshima M and Ward J (1986). Dietary iodine deficiency as a tumor promoter and carcinogen in male F344/NCr rats. *Cancer Res,* **46,** 877–83.

Olsen JH, Garwicz S, Hertz H, Jonmundsson G, Langmark F, Lanning M, et al (1993). Second malignant neoplasms after cancer in childhood or adolescence. *Br Med J,* **307,** 1030–36.

Omar RZ, Barber JA and Smith PG (1999). Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br J Cancer,* **79,** 1288–301.

Ozaki T, Schaefer KL, Wai D, Yokoyama R, Ahrens S, Diallo R, et al (2002). Population-based genetic alterations in Ewing's tumors from Japanese and European Caucasian patients. *Ann Oncol,* **13,** 1656–64.

Palmer JP and Spratt DW (1956). Pelvic carcinoma following irradiation for benign gynecological disease. *Am J Obstet Gynecol,* **72,** 497–505.

Park Y, Hunter DJ, Spiegelman D, Bergkvist L, Berrino F, van den Brandt PA, et al (2005). Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. *J Am Med Assoc,* **294,** 2849–57.

Parkin DM (2006). The global health burden of infection-associated cancers in the year 2002. *Int J Cancer,* **118,** 3030–44.

Parkin DM, Whelan SL, Ferlay J, Teppo L and Thomas DB (2002). *Cancer Incidence in Five Continents,* Volume VIII. IARC Scientific Publication No. 155. Lyon, International Agency for Research on Cancer.

Parkin DM, Whelan SL, Ferlay J and Storm H (2005). *Cancer Incidence in Five Continents,* Volumes I to VIII. IARC Cancer Base No. 7. Lyon, International Agency for Research on Cancer. Available at www-dep.iarc.fr/

Pavia M, Bianco A, Pileggi C and Angelillo IF (2003). Meta-analysis of residential exposure to radon gas and lung cancer. *Bull World Health Organ,* **81,** 732–8.

Pawlish KS, Schottenfeld D, Severson R and Montie JE (1997). Risk of multiple primary cancers in prostate cancer patients in the Detroit metropolitan area: a retrospective cohort study. *Prostate,* **33**(2), 75–86.

Percy C, Ries LG and van Holten VD (1990). The accuracy of liver cancer as the underlying cause of death on death certificates. *Public Health Rep,* **105,** 361–7.

Pickles T and Phillips N (2002). The risk of second malignancy in men with prostate cancer treated with or without radiation in British Columbia, 1984–2000. *Radiother Oncol,* **65**(3), 145–51.

Pierce DA and Preston DL (2000). Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res,* **154,** 178–86.

Pierce DA and Vaeth M (1991). The shape of the cancer mortality dose–response curve for the A-bomb survivors. *Radiat Res,* **126,** 36–42.

Pierce DA, Stram DO and Vaeth M (1990). Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res,* **123,** 275–84.

Pierce DA, Stram DO, Vaeth M, et al (1992). The errors-in-variables problem: considerations provided by radiation dose–response analyses of the A-bomb survivor data. *J Am Stat Assoc,* **87,** 351–9.

Pierce DA, Shimizu Y, Preston DL, Vaeth M and Mabuchi K (1996). Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat Res,* **146**(1), 1–27.

Pierce DA, Sharp GB and Mabuchi K (2003). Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat Res,* **159,** 511–20.

Porstendorfer J and Reineking A (1999). Radon: characteristics in air and dose conversion factors. *Health Phys,* **76,** 300–305.

Pottern LM, Kaplan MM, Larsen PR, Silva JE, Koenig RJ, Lubin JH, et al (1990). Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. *J Clin Epidemiol,* **43,** 449–60.

Preston DL, Lubin JH, Pierce DA and McConney ME (1993). *Epicure Users Guide.* Seattle WA, Hirosoft International Corporation.

Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al (1994). Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat Res,* **137**(2 Suppl), S68–S97. Erratum in *Radiat Res,* **139,** 129.

Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG and Boice JD Jr (2002a). Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res,* **158,** 220–35.

Preston DL, Ron E, Yonehara S, Kobuke T, Fujii H, Kishikawa M, et al (2002b). Tumors of the nervous system and pituitary gland associated with atomic bomb radiation exposure. *J Natl Cancer Inst,* **94,** 1555–63.

Preston DL, Shimizu Y, Pierce DA, Suyama A and Mabuchi K (2003). Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res,* **160,** 381–407.

Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S and Kodama K (2004). Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res,* **162,** 377–89.

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al (2007). Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res,* **168,** 1–64.

Preston DL, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, et al (2008). Solid cancer incidence in atomic bomb survivors exposed *in utero* or as young children. *J Natl Cancer Inst,* **100,** 428–36.

Preston-Martin S, Thomas DC, White SC and Cohen D (1988). Prior exposure to medical and dental X-rays related to tumours of the parotid gland. *J Natl Cancer Inst,* **80,** 943–9.

Preston-Martin S, Munir R and Chakrabarti I (2006). Nervous system. In *Cancer Epidemiology and Prevention* (Third Edition), pp1196–229 (D Schottenfeld and JF Fraumeni, eds). New York, Oxford University Press.

Pukkala E, Aspholm R, Auvinen A, Eliasch H, Gundestrup M, Haldorsen T, et al (2002). Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. *Br Med J,* **325,** 567.

Quinn M and Babb P (2000). Cancer trends in England and Wales 1950–1999. *Health Stat Q,* **8,** 5–19.

Radford EP and Renard KG (1984). Lung cancer in Swedish iron miners exposed to low doses of radon daughters. *N Engl J Med,* **310,** 1485–94.

Rahu M, Rahu K, Auvinen A, Tekkel M, Stengrevics A, Hakulinen T, Boice JD Jr and Inskip PD (2006). Cancer risk among Chernobyl cleanup workers in Estonia and Latvia, 1986–1998. *Int J Cancer,* **119**(1), 162–8.

Rajaraman P, Sigurdson AJ, Doody MM, Freedman DM, Hauptmann M, Ron E, et al (2006). Lung cancer risk among US radiologic technologists, 1983–1998. *Int J Cancer,* **119,** 2481–6.

Rallison ML, Lotz T, Bishop M, Divine W, Haywood K, Lyon J, et al (1990). Cohort study of thyroid disease near the Nevada test site: a preliminary report. *Health Phys,* **59,** 739–46.

Richardson DB (2009). Exposure to ionizing radiation in adulthood and thyroid incidence. *Epidemiology,* **20**(2), 191–7.

Richardson DB and Wing S (2006). Lung cancer mortality among workers at a nuclear materials fabrication plant. *Am J Ind Med,* **49,** 102–11.

Rinsky RA, Zumwalde RD, Waxweiler RJ, Murray WE Jr, Bierbaum PJ, Landrigan PJ, et al (1981). Cancer mortality at a naval nuclear shipyard. *Lancet,* **1,** 231–5.

Ritz B (1999). Radiation exposure and cancer mortality in uranium processing workers. *Epidemiology,* **10,** 531–38.

Ritz B, Morgenstern H, Crawford-Brown D and Young B (2000). The effects of internal radiation exposure on cancer mortality in nuclear workers at Rocketdyne/Atomics International. *Environ Health Perspect,* **108,** 743–51.

Robbins J and Adams W (1989). Radiation effects in the Marshall Islands. In *Radiation and the Thyroid,* pp11–24 (S Nagataki, ed). Tokyo, Excepta Medica.

Roesch WC (ed) (1987). US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Volume 1. Hiroshima, Radiation Effects Research Foundation.

Rogel A, Carre N, Amoros E, Bonnet-Belfais M, Goldberg M, Imbernon E, Calvez T and Hill C (2005). Mortality of workers exposed to ionizing radiation at the French National Electricity Company. *Am J Ind Med,* **47,** 72–82.

Ron E, Modan B and Boice JD Jr (1988). Mortality after radiotherapy for ringworm of the scalp. *Am J Epidemiol,* **127,** 713–25.

Ron E, Modan B, Preston D, Alfandary E, Stovall M and Boice JD Jr (1989). Thyroid neoplasia following low-dose radiation in childhood. *Radiat Res,* **120,** 516–31.

Ron E, Modan B, Preston D, Alfandary E, Stovall M and Boice JD Jr (1991). Radiation-induced skin carcinomas of the head and neck. *Radiat Res,* **125,** 318–25.

Ron E, Carter R, Jablon S and Mabuchi K (1994). Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology,* **5,** 48–56.

Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al (1995). Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res,* **141,** 259–77.

Ron E, Doody MM, Becker DV, Brill AB, Curtis RE, Goldman MB, et al (1998). Cancer mortality following treatment for adult hyperthyroidism. *J Am Med Assoc,* **280,** 347–55.

Ron E, Ikeda T, Preston DL and Tokuoka S (2005). Male breast cancer incidence among atomic bomb survivors. *J Natl Cancer Inst,* **97,** 603–5.

Ronckers CM, Erdmann CA and Land CE (2005). Radiation and breast cancer: a review of current evidence. Breast *Cancer Res,* **7,** 21–32.

Ronckers CM, Sigurdson AJ, Stovall M, Smith SA, Mertens AC, Liu Y, et al (2006). Thyroid cancer in childhood cancer survivors: a detailed evaluation of radiation dose response and its modifiers. *Radiat Res,* **166,** 618–28.

Rooney C, Beral V, Maconochie N, Fraser P and Davies G (1993). Case–control study of prostatic cancer in employees of the United Kingdom Atomic Energy Authority. *Br Med J,* **307,** 1391–7.

Rowland RE (1995). Dose–response relationships for female radium dial workers: a new look. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium,* pp135–43 (G Van Kaick et al, eds). Singapore, World Scientific.

Rowland RE, Stehney AF and Lucas HF Jr (1978). Dose–response relationships for female radium dial workers. *Radiat Res,* **76,** 368–83.

Rubino C, De Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C and Schlumberger M (2003). Second primary malignancies in thyroid cancer patients. *Br J Cancer,* **89,** 1638–44.

Rubino C, Shamsaldin A, Lê MG, Labbé M, Guinebretière JM, Chavaudra J and de Vathaire F (2005). Radiation dose and risk of soft tissue and bone sarcoma after breast cancer treatment. *Breast Cancer Res Treat,* **89,** 277–88.

Ryberg M, Lundell M, Nilsson B and Petterson F (1990). Malignant disease after radiation treatment for benign gynaecological disorders. A study of a cohort of metropathia patients. *Acta Oncol,* **29**(5), 563–7.

Sack RB, Gyr K and Leon-Barua R (1997). Proceedings of the Second International Workshop on *Helicobacter pylori* infections in the developing world. Lima, Peru, 28–31 January 1996. Introduction. *Clin Infect Dis,* **25**(5), 971–2.

Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B and Novikov I (2005). Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. *Radiat Res,* **163,** 424–32.

Sadetzki S, Chetrit A, Lubina A, Stovall M and Novikov I (2006). Risk of thyroid cancer after childhood exposure to ionizing radiation for tinea capitis. *J Clin Endocrinol Metab,* **91,** 4798–804.

Samet JM, Pathak DR, Morgan MV, Key CR, Valdivia AA and Lubin JH (1991). Lung cancer mortality and exposure to radon progeny in a cohort of New Mexico uranium miners. *Health Phys,* **61**(6), 745–52.

Sandhu MS, White IR and McPherson K (2001). Systematic review of the prospective cohort studies on meat consumption and colorectal cancer risk: a meta-analytical approach. *Cancer Epidemiol Biomarkers Prev,* **10,** 439–46.

Sawant SG, Randers-Pehrson G, Geard CR, Brenner DJ and Hall EJ (2001). The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T½ cells *in vitro* can be initiated in the unirradiated neighbors of irradiated cells. *Radiat Res,* **155,** 397–401.

Schneider AB, Shore-Freedman E, Ryo UY, Bekerman C, Favus M and Pinsky S (1985). Radiation-induced tumors of the head and neck following childhood irradiation. *Medicine,* **64,** 1–15.

Schneider AB, Ron E, Lubin J, Stovall M and Gierlowski TC (1993). Dose–response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. *J Clin Endocrinol Metab,* **77,** 362–4.

Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, et al (1998). Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose–response relationships. *Radiat Res,* **149,** 625–30.

Schneider AB, Ron E, Lubin J, Stovall M, Shore-Freedman E, Tolentino J and Collins BJ (2008). Acoustic neuromas following childhood radiation treatment for benign conditions of the head and neck. *Neuro Oncol,* **10,** 73–8.

Schwartzbaum JA, Fisher JL, Aldape KD and Wrensch M (2006). Epidemiology and molecular pathology of glioma. *Nat Clin Pract Neurol,* **2,** 494–503.

Shakhtarin VV, Tsyb AF, Stepanenko VF, Orlov MY, Kopecky KJ and Davis S (2003). Iodine deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents in the Bryansk region of Russia following the Chernobyl power station accident. *Int J Epidemiol,* **32,** 584–91.

Sharp GB, Mizuno T, Cologne JB, Fukuhara T, Fujiwara S, Tokuoka S and Mabuchi K (2003). Hepatocellular carcinoma among atomic bomb survivors: significant interaction of radiation with hepatitis C virus infections. *Int J Cancer,* **103,** 531–7.

Shilnikova NS, Preston DL, Ron E, Gilbert ES, Vassilenko EK, Romanov SA, et al (2003). Cancer mortality risk among workers at the Mayak nuclear complex. *Radiat Res,* **159,** 787–98.

Shimizu Y, Kato H and Schull WJ (1988). Life Span Study Report 11, Part II: Cancer Mortality in the Years 1950–1985 based on the Recently Revised Doses (DS86). Report TR5-88. Hiroshima, Radiation Effects Research Foundation,

Shore RE (1990). Overview of radiation-induced skin cancer in humans. *Int J Radiat Biol,* **57,** 809–27.

Shore RE (1992). Issues and epidemiological evidence regarding radiation-induced thyroid cancer. *Radiat Res,* **131,** 98–111.

Shore RE, Hildreth N, Woodard E, Dvoretsky P, Hempelmann L and Pasternack B (1986). Breast cancer among women given X-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst,* **77,** 689–96.

Shore RE, Hildreth N, Dvoretsky P, Andresen E, Moseson M and Pasternack B (1993). Thyroid cancer among persons given X-ray treatment in infancy for an enlarged thymus gland. *Am J Epidemiol,* **137,** 1068–80.

Shore RE, Moseson M, Xue X, Tse Y, Harley N and Pasternack BS (2002). Skin cancer after X-ray treatment for scalp ringworm. *Radiat Res,* **157,** 410–18.

Shore RE, Moseson M, Harley N and Pasternack BS (2003). Tumors and other diseases following childhood X-ray treatment for ringworm of the scalp (tinea capitis). *Health Phys,* **85,** 404–8.

Shrimpton P, Hillier MC, Lewis MA and Dunn M (2003). Doses from Computed Tomography (CT) Examinations in the UK – 2003 Review. Chilton, NRPB-W67. Available at www.hpa.org.uk

Sigurdson AJ, Doody MM, Rao RS, Freedman DM, Alexander BH, Hauptmann M, et al (2003). Cancer incidence in the US radiologic technologists health study, 1983–1998. *Cancer,* **97,** 3080–89.

Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, et al (2005). Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case–control study. *Lancet,* **365,** 2014–23.

Silver SR, Daniels RD, Taulbee TD, Zaebst DD, Kinnes GM, Couch JR, et al (2004). Differences in mortality by radiation monitoring status in an expanded cohort of Portsmouth naval shipyard workers. *J Occup Environ Med,* **46,** 677–90.

Silverman DT, Morrison AS and Devesa SS (1996). Bladder cancer. In *Cancer Epidemiology and Prevention* (Second Edition), pp1156–79 (D Schottenfeld and JF Fraumeni Jr, eds). New York, Oxford University Press.

Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, Vasilenko EK and Koshurnikova NA (2008). Lung, liver and bone cancer mortality in Mayak workers. *Int J Cancer,* **123**, 905–11.

Sont WN, Zielinski JM, Ashmore JP, Jiang H, Krewski D, Fair ME, et al (2001). First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol,* **153,** 309–18.

Spiess H (1995). The Ra-224 study: past, present and future. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium,* pp157–63 (G Van Kaick et al, eds). Singapore, World Scientific.

Stather JW, Muirhead CR, Edwards AA, Harrison JD, Lloyd DC and Wood NR (1988). Health Effects Models Developed from the 1988 UNSCEAR Report. Chilton, NRPB-R226.

Stebbings JH, Lucas HF and Stehney AF (1984). Mortality from cancers of major sites in female radium dial workers. *Am J Ind Med,* **5,** 435–59.

Stebbings JH and Semkiw W (1989). Central nervous system tumours and related intracranial pathologies in radium dial workers. In *Risks from Radium and Thorotrast,* pp63–7 (DM Taylor et al, eds). BIR Report 21. London, British Institute of Radiology.

Stehney AF (1995). Survival times of pre-1950 US women radium dial workers. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium,* pp149–55 (G Van Kaick et al, eds). Singapore, World Scientific.

Stewart AM and Kneale GW (2000). A-bomb survivors: factors that may lead to a re-assessment of the radiation hazard. *Int J Epidemiol,* **29,** 708–14.

Stewart AM, Webb KW and Hewitt D (1958). A survey of childhood malignancies. *Br Med J,* **1,** 1495–508.

Stewart BW and Kleihues P (eds) (2003). *World Cancer Report.* Lyon, International Agency for Research on Cancer.

Storm HH, Andersson M, Boice JD Jr, Blettner M, Stovall M, Mouridsen HT, et al (1992). Adjuvant radiotherapy and risk of contralateral breast cancer. *J Natl Cancer Inst,* **84,** 1245–50.

Straume T, Egbert SD, Woolson WA, Finkel RC, Kubik PW, Gove HE, et al (1992). Neutron discrepancies in the DS86 Hiroshima dosimetry system. *Health Phys,* **63,** 421–6.

Strom DJ, Reif RH, Andrews DA, et al (1996). Occupational Exposure to Radon and Thoron. US Department of Energy Radiological Control Coordinating Committee. Radon Subcommittee. PNNL Report 14108.

Sun Q, Akiba S, Tao Z, Yuan Y, Zou J, Morishima H, et al (2000). Excess relative risk of solid cancer mortality after prolonged exposure to naturally occurring high background radiation in Yangjiang, China. *J Radiat Res,* **41**(Suppl), 43–52.

Takahashi T, Fujimori K, Simon SL, Bechtner G, Edwards R and Trott KR (1999). Thyroid nodules, thyroid function and dietary iodine in the Marshall Islands. *Int J Epidemiol,* **28**(4), 742–9.

Takahashi T, Trott KR, Fujimori K, et al (2001). *Thyroid Disease in the Marshall Islands. Findings from 10 Years of Study.* Sendai, Japan, Tohoku University Press.

Takahashi T, Schoemaker MJ, Trott KR, Simon SL, Fujimori K, Nakashima N, et al (2003). The relationship of thyroid cancer with radiation exposure from nuclear weapon testing in the Marshall Islands. *J Epidemiol,* **13,** 99–107.

Tao Z, Zha Y, Akiba S, Sun Q, Zou J, Li J, et al (2000). Cancer mortality in the high background radiation area of Yangjiang, China during the period between 1979 and 1995. *J Radiat Res,* **41**(Suppl), 31–41.

Tavani A, Negri E, Franceschi S and La Vecchia C (1993). Risk factors for esophageal cancer in women in northern Italy. *Cancer,* **72,** 2531–6.

Telle-Lamberton M, Samson E, Caër S, Bergot D, Bard D, Bermann F, et al (2007). External radiation exposure and mortality in a cohort of French nuclear workers. *Occup Environ Med,* **64,** 694–70.

Thomas GA and Williams ED (1991). Evidence for and possible mechanisms of non-genotoxic carcinogenesis in the rodent thyroid. *Mutat Res,* **248,** 357–70.

Thomas D, Stram D and Dwyer J (1993). Exposure measurement error: influence on exposure-disease. Relationships and methods of correction. *Annu Rev Public Health,* **14,** 69–93.

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al (1994). Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958–1987. *Radiat Res,* **137**(Suppl), S17–S67. Erratum in *Radiat Res,* **139,** 129.

Tomasek L, Palcek V, Muller T, Heribanova A, Matzner J, Burian I and Holecek J (2003). Czech studies of lung cancer risk from radon. *Int J Low Radiat,* **1,** 50–62.

Travis LB, Curtis RE, Glimelius B, Holowaty EJ, Van Leeuwen FE, Lynch CF, et al (1995). Bladder and kidney cancer following cyclophosphamide therapy for non-Hodgkin's lymphoma. *J Natl Cancer Inst,* **87,** 524–31.

Travis LB, Curtis RE, Boice JD Jr, Platz CE, Hankey BF and Fraumeni JF Jr (1996). Second malignant neoplasms among long-term survivors of ovarian cancer. *Cancer Res,* **56,** 1564–70.

Travis LB, Curtis RE, Storm H, Hall P, Holowaty E, Van Leeuwen FE, et al (1997). Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J Natl Cancer Inst,* **89,** 1429–39.

Travis LB, Gospodarowicz M, Curtis RE, Clarke EA, Andersson M, Glimelius B, et al (2002). Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. *J Natl Cancer Inst,* **94,** 182–92.

Travis LB, Hill DA, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al (2003a). Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *J Am Med Assoc,* **290,** 465–75.

Travis LB, Hauptmann M, Gaul LK, Storm HH, Goldman MB, Nyberg U, et al (2003b). Site-specific cancer incidence and mortality after cerebral angiography with radioactive Thorotrast. *Radiat Res,* **160,** 691–706.

Travis LB, Hill D, Dores GM, Gospodarowicz M, van Leeuwen FE, Holowaty E, et al (2005a). Cumulative absolute breast cancer risk for young women treated for Hodgkin lymphoma. *J Natl Cancer Inst,* **97,** 1428–37.

Travis LB, Fosså SD, Schonfeld SJ, McMaster ML, Lynch CF, Storm H, et al (2005b). Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst,* **97,** 1354–65.

Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, Brill AB, et al (2006). A cohort study of thyroid cancer and other thyroid diseases after the Chornobyl accident: thyroid cancer in Ukraine detected during first screening. *J Natl Cancer Inst,* **98,** 897–903.

Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, et al (1987). Bone sarcomas linked to radiotherapy and chemotherapy in children. *N Engl J Med,* **317,** 588–93.

Tucker MA, Jones PH, Boice JD Jr, Robison LL, Stone BJ, Stovall M, et al (1991). Therapeutic radiation at a young age is linked to secondary thyroid cancer. *Cancer Res,* **51,** 2885–8.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1958). Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. Official Records of the General Assembly, Thirteenth Session, Supplement No.17 (A/3838). New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1988). Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 1988 Report to the General Assembly, with annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1993). Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1994). Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000). Sources and Effects of Ionizing Radiation. Vol. II: Effects. UNSCEAR 2000 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2001). Hereditary Effects of Radiation. UNSCEAR 2001 Report to the General Assembly, with scientific annex. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2008). Effects of Ionizing Radiation. UNSCEAR 2006 Report to the General Assembly, with scientific annexes. New York, United Nations.

van Kaick G, Welsch H, Luehrs H, et al (1989). The German Thorotrast study – report on 20 years follow-up. In *Risks from Radium and Thorotrast,* pp98–104 (DM Taylor et al, eds). BIR Report 21. London, British Institute of Radiology.

van Kaick G, Welsch H, Luehrs H, et al (1995). Epidemiological results and dosimetric calculations - an update of the German Thorotrast study. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium,* pp171–75 (G van Kaick et al, eds). Singapore, World Scientific.

van Kaick G, Dalheimer A, Hornik S, Kaul A, Liebermann D, Lührs H, et al (1999). The German Thorotrast study: recent results and assessment of risks. *Radiat Res,* **152,** S64–S71.

van Leeuwen FE, Klokman WJ, Stovall M, Hagenbeek A, van den Belt-Dusebout AW, Noyon R, et al (1995). Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J Natl Cancer Inst,* **87,** 1530–37.

van Leeuwen FE, Klokman WJ, Stovall M, Dahler EC, van't Veer MB, Noordijk EM, et al (2003). Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst,* **95,** 971–80.

Villeneuve PJ, Morrison HI and Lane R (2007). Radon and lung cancer risk: an extension of the mortality follow-up of the Newfoundland fluorspar cohort. *Health Phys,* **92,** 157–69.

Vrijheid M, Cardis E, Blettner M, Gilbert E, Hakama M, Hill C, et al (2007). The 15-country collaborative study of cancer risk among radiation workers in the nuclear industry: design, epidemiological methods and descriptive results. *Radiat Res,* **167,** 361–79.

Wagoner JK (1984). Leukemia and other malignancies following radiation therapy for gynecological disorders. In *Radiation Carcinogenesis: Epidemiology and Biological Significance* (JD Boice and JF Fraumeni, eds). New York, Raven Press.

Wakeford R (2004). The cancer epidemiology of radiation. *Oncogene,* **23,** 6404–28.

Walsh L, Rühm W and Kellerer AM (2004). Cancer risk estimates for gamma-rays with regard to organ-specific doses. Part II: site-specific solid cancers. *Radiat Environ Biophys,* **43,** 225–31.

Wang JX, Zhang LA, Li BX, Zhao YC, Wang ZQ, Zhang JY and Aoyama T (2002). Cancer incidence and risk estimation among medical X-ray workers in China, 1950–1995. *Health Phys,* **82,** 455–66.

Watson SJ, Jones AL, Oatway WB and Hughes JS (2005). Ionising Radiation Exposure of the UK Population: 2005 Review. Chilton, HPA-RPD-001. Available at www.hpa.org.uk

Weiss HA, Darby SC and Doll R (1994). Cancer mortality following X-ray treatment for ankylosing spondylitis. *Int J Cancer,* **59,** 327–38.

West J, Wood H and Logan RFA (2006). Trends in the incidence of primary liver and biliary tract cancers in England and Wales 1971–2001. *Br J Cancer,* **94,** 1751–8.

Wick RR, Chmelevsky D and Gössner W (1995). Current status of the follow-up of radium-224 treated ankylosing spondylitis patients. In *Health Effects of Internally Deposited Radionuclides: Emphasis on Radium and Thorium,* pp165–9 (G van Kaick et al, eds). Singapore, World Scientific.

Wick RR, Nekolla EA, Gössner W and Kellerer AM (1999). Late effects in anklylosing spondylitis patients treated with ^{224}Ra. *Radiat Res,* **152**(6 Suppl), S8–S11.

Wiggs LD, Cox-DeVore CA and Voelz GL (1991). Mortality among a cohort of workers monitored for ^{210}Po exposure: 1944–1972. *Health Phys,* **61**(1), 71–6.

Wiggs LD, Johnson ER, Cox-DeVore CA and Voelz GL (1994). Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposure to plutonium and external ionizing radiation. *Health Phys,* **67,** 577–88.

Wilkinson GS, Tietjen GL, Wiggs LD, Galke WA, Acquavella JF, Reyes M, et al (1987). Mortality among plutonium and other radiation-exposed workers at a plutonium weapons facility. *Am J Epidemiol,* **125,** 231–50.

Wilson RT, Moore LE and Dosemeci M (2004). Occupational exposures and salivary gland cancer mortality among African American and white workers in the United States. *J Occup Environ Med,* **46,** 287–97.

Wing S and Richardson DB (2005). Age at exposure to ionising radiation and cancer mortality among Hanford workers: follow up through 1994. *Occup Environ Med,* **62,** 465–72.

Wing S, Richardson D, Wolf S and Mihlan G (2004). Plutonium-related work and cause-specific mortality at the United States Department of Energy Hanford Site. *Am J Ind Med,* **45,** 153–64.

Wolden SL, Lamborn KR, Cleary SF, Tate DJ and Donaldson SS (1998). Second cancers following pediatric Hodgkin's disease. *J Clin Oncol,* **16,** 536–44.

Wong FL, Boice JD Jr, Abramson DH, Tarone RE, Kleinerman RA, Stovall M, et al (1997). Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. *J Am Med Assoc,* **278,** 1262–7.

Woodward A, Roder D, McMichael AJ, Crouch P and Mylvaganam A (1991). Radon daughter exposures at the Radium Hill uranium mine and lung cancer rates among former workers, 1952–87. *Cancer Causes Control,* **2,** 213–20.

Wrixon AD, Green BMR, Lomas PR, Miles JCH, Cliff KD, Francis EA, et al (1988). Natural Radiation Exposure in UK Dwellings. Chilton, NRPB-R190.

Xuan XZ, Lubin JH, Li JY, Yang LF, Luo AS, Lan Y, et al (1993). A cohort study in southern China of tin miners exposed to radon and radon decay products. *Health Phys,* **64,** 120–31.

Yiin JH, Schubauer-Berigan MK, Silver SR, Daniels RD, Kinnes GM, Zaebst DD, et al (2005). Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth Naval Shipyard. *Radiat Res,* 1**63,** 603–13.

Yiin JH, Silver SR, Daniels RD, Zaebst DD, Seel EA and Kubale TL (2007). A nested case–control study of lung cancer risk and ionizing radiation exposure at the Portsmouth naval shipyard. *Radiat Res,* **168,** 341–8.

Yonehara S, Brenner AV, Kishikawa M, Inskip PD, Preston DL, Ron E, et al (2004). Clinical and epidemiologic characteristics of first primary tumors of the central nervous system and related organs among atomic bomb survivors in Hiroshima and Nagasaki, 1958–1995. *Cancer,* **101,** 1644–54.

Yoshinaga S, Hauptmann M, Sigurdson AJ, Doody MM, Freedman DM, Alexander BH, et al (2005). Nonmelanoma skin cancer in relation to ionizing radiation exposure among US radiologic technologists. *Int J Cancer,* **115,** 828–34.

Yoshinaga S, Mabuchi K, Sigurdson AJ, Doody MM and Ron E (2004). Cancer risks among radiologists and radiologic technologists: review of epidemiologic studies. *Radiology,* **233,** 313–21.

Young KC, Burch A and Oduko JM (2005). Radiation doses received in the UK Breast Screening Programme in 2001 and 2002. *Br J Radiol,* **78**(927), 207–18.

Young RW and Kerr GD (eds) (2005). Report of the Joint US–Japan Working Group. Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki. Hiroshima, Radiation Effects Research Foundation.

Zabel EW, Alexander BH, Mongin SJ, Doody MM, Sigurdson AJ, Linet MS, et al (2006). Thyroid cancer and employment as a radiologic technologist. *Int J Cancer,* **119,** 1940–45.

Zablotska LB, Ashmore JP and Howe GR (2004). Analysis of mortality among Canadian nuclear power industry workers after chronic low-dose exposure to ionizing radiation. *Radiat Res,* **161,** 633–41.

Zablotska LB, Chak A, Das A and Neugut AI (2005). Increased risk of squamous cell esophageal cancer after adjuvant radiation therapy for primary breast cancer. *Am J Epidemiol,* **161,** 330–37.

Zeeb H, Blettner M, Langner I, Hammer GP, Ballard TJ, Santaquilani M, et al (2003). Mortality from cancer and other causes among airline cabin attendants in Europe: a collaborative cohort study in eight countries. *Am J Epidemiol,* **158,** 35–46.

Appendix A
Measures of Population Radiation Risk

Fundamental to calculation of measures of population risk is the estimation of the *instantaneous cancer mortality rate*, $\mu_c(s,t \mid a,D)$, expressed as cancer deaths per year, that will result for a given cancer type c, at age t for persons of sex s following some instantaneously administered radiation dose D given at age a. This is typically evaluated by fitting a model for radiation risk to data corresponding to some exposed cohort. For example, the *generalised relative risk model* assumes that the mortality rate for cancer type c at age t, y years after instantaneous exposure to a radiation dose D administered at age a (so that $t = a + y$) is given by $\mu_c(s,t \mid a,D) = \mu_c(s,t) \cdot [1 + ERR_c(s,a,y,D)]$. Similar models can be fitted to cancer incidence data. Typically the radiation dose–response term can be multiplicatively separated from the temporal modifiers in this expression, eg $\mu_c(s,t \mid a,D) = \mu_c(s,t) \cdot [1 + F_c(D) \cdot \varphi_c(s,a,y)]$. For example, the linear-quadratic-exponential expression $F_c(D) = (\alpha \cdot D + \beta \cdot D^2) \cdot \exp(\gamma \cdot D)$ might be used as the form of dose response (a model suggested by much radiobiological data; UNSCEAR, 1993), and some empirical exponential function, $\varphi_c(s,a,y) = \exp(\kappa_0 + \kappa_1 \cdot s + \kappa_2 \cdot a + \kappa_3 \cdot y)$, as the temporal modifier term.

Once a model for radiation risk has been developed, it is in principle straightforward to use it to estimate the burden of cancer in some hypothetically exposed population. Fundamental to assessment of cancer risk in such a population, it is necessary to assume 'background' or 'underlying' mortality rates, $\mu_c(s,t)$, that this population will experience in the absence of radiation exposure, both overall and for each cancer type. For calculations of cancer risk, cancer incidence must also be specified. These background rates are generally estimated from national morbidity and mortality rates. It is usual to calculate the consequence of an instantaneous exposure to a 'test' dose, D_t, that is assumed to be administered at age a. However, other more general patterns of exposure are possible, and may be derived by obvious generalisations of the calculations below. There are six commonly used measures of population cancer risk, largely reviewed elsewhere (Thomas et al, 1992; Little et al, 1999; Bennett et al, 2004). The first measure is *excess cancer deaths* (ECD) per unit dose:

$$\mathrm{ECD}_c(s,a,D_t) = \frac{\int_a^{y_T} \mu_c(s,t \mid a,D_t) \cdot S_c(s,t \mid a,D_t)\, \mathrm{d}t - \int_a^{y_T} \mu_c(s,t) \cdot S(s,t \mid a)\, \mathrm{d}t}{D_t} \qquad \text{(A1)}$$

where $\mu_c(s,t \mid a,D_t)$ is the instantaneous cancer mortality rate (cancers per year) for cancer type c, at age t for persons of sex s following the assumed dose D_t, given at age a. As above, this is evaluated by some model fitted to data. $S_c(s,t \mid a,D_t)$ is the fraction of the population of sex s alive at age a who

remain alive at age t (> a), and can be estimated by $S_c(s,t \mid a,D_t) = \exp\left[-\int_a^t \mu(s,w \mid a,D_t)\,\mathrm{d}w\right]$, where $\mu(s,t \mid a,D_t) = \mu_c(s,t \mid a,D_t) + \sum_{l \neq c} \mu_l(s,t)$ is the all-cause mortality rate, a summation over the specific cancer type of interest, and all other cancer and non-cancer causes of death. $S(s,t) = S_c(s,t \mid a,0)$ is the analogous survival probability at zero radiation dose. If a generalised relative risk model were to be fitted, in which for cancer type c the mortality rate at age t, y years after exposure to a dose D_t administered at age a (= $t - y$) is given by $\mu_c(s,t \mid a,D_t) = \mu_c(s,t) \cdot [1 + \mathrm{ERR}_c(s,a,y,D_t)]$ then this risk can be written as

$$\mathrm{ECD}_c(s,a,D_t) = \frac{\left\{\begin{array}{l}\int_a^{y_T} \mu_c(s,t) \cdot [1+\mathrm{ERR}_c(s,a,t-a,D_t)] \cdot S(s,t) \cdot \exp\left[-\int_a^t \mu_c(s,w) \cdot \mathrm{ERR}_c(s,a,w-a,D_t)\,\mathrm{d}w\right]\mathrm{d}t \\ -\int_a^{y_T} \mu_c(s,t) \cdot S(s,t)\,\mathrm{d}t\end{array}\right\}}{D_t} \tag{A2}$$

Persons are assumed capable of surviving in principle up to the age of y_T, at which point they are assumed to die instantaneously (ie the population is truncated at that age). The particular y_T used does not much matter as long as it is sufficiently large. Little et al (1999) used a value of 121 years, as did Bennett et al (2004). This measure has been used by the BEIR V Committee (1990) and elsewhere (Little et al, 1992, 1997, 1999). A very similar measure, the *excess cancer incidence* (ECI) per unit dose, can also be calculated:

$$\mathrm{ECI}_c(s,a,D_t) = \frac{\int_a^{y_T} \mu i_c(s,t \mid a,D_t) \cdot \mathrm{SI}_c(s,t \mid a,D_t)\,\mathrm{d}t - \int_a^{y_T} \mu i_c(s,t) \cdot \mathrm{SI}\,(s,t \mid a,D_t)\,\mathrm{d}t}{D_t} \tag{A3}$$

where $\mu i_c(s,t \mid a,D_t)$ is the instantaneous cancer incidence rate (cancers per year) for cancer type c, at age t for persons of sex s following the assumed dose D_t, given at age a, and

$\mathrm{SI}_c(s,t \mid a,D_t) = \exp\left[-\int_a^t \mu i\,(s,w \mid a,D_t)\,\mathrm{d}w\right]$, where $\mu i\,(s,t \mid a,D_t) = \mu i_c(s,t \mid a,D_t) + \sum_{l \neq c} \mu_l(s,t)$.

A population risk measure closely related to the ECD is the *risk of exposure-induced death* (REID) per unit dose:

$$\mathrm{REID}_c(s,a,D_t) = \frac{\int_a^{y_T} [\mu_c(s,t \mid a,D_t) - \mu_c(s,t)] \cdot S_c(s,t \mid a,D_t)\,\mathrm{d}t}{D_t} \tag{A4}$$

As above, when a generalised relative risk model $\mu_c(s,t \mid a,D_t) = \mu_c(s,t)\cdot[1+\mathrm{ERR}_c(s,a,y,D_t)]$ is assumed, this reduces to:

$$\mathrm{REID}_c(s,a,D_t) = \frac{\int_a^{y_T} \mu_c(s,t)\cdot \mathrm{ERR}_c(s,a,t-a,D_t)\cdot S(t,a)\cdot \exp\left[-\int_a^t \mu_c(s,w)\cdot \mathrm{ERR}_c(s,a,w-a,D_t)\,\mathrm{d}w\right]\mathrm{d}t}{D_t} \quad \text{(A5)}$$

This risk measure has been employed by many scientific committees (ICRP, 1991; UNSCEAR, 1994, 2000) and others (Little et al, 1992, 1997, 1999), and is arguably the most commonly used such summary risk measure. The ECD measure, which is calculated by taking the difference between the numbers of cancers that would occur in an irradiated population and in an otherwise equivalent unirradiated population, in general gives a somewhat lower value than the REID measure. This is immediate from equation A1, since we may write:

$$\mathrm{ECD}_c(s,a,D_t) = \frac{\int_a^{y_T} [\mu_c(s,t \mid a,D_t) - \mu_c(s,t)]\cdot S_c(s,t \mid a,D_t)\,\mathrm{d}t - \int_a^{y_T} \mu_c(s,t)\cdot[S(s,t \mid a) - S_c(s,t \mid a,D_t)]\,\mathrm{d}t}{D_t}$$

$$= \mathrm{REID}_c(s,a,D_t) - \frac{\int_a^{y_T} \mu_c(s,t)\cdot[S(s,t \mid a) - S_c(s,t \mid a,D_t)]\,\mathrm{d}t}{D_t} \quad \text{(A6)}$$

The second term in the right-hand side of this expression is the number of people that would have died from cancer anyway among that fraction of the population that die from radiation-induced cancer. In other words, the REID is generally greater than the ECD because the former quantity does not include that fraction (about 20% for the general population in equilibrium) of the people developing a fatal radiation-induced cancer who would have died from some sort of cancer anyway. The analogous quantity calculated for cancer incidence, *risk of exposure-induced cancer incidence* (REIC) per unit dose, can also be defined, and has been used by some (Bennett et al, 2004). This is given by

$$\mathrm{REIC}_c(s,a,D_t) = \frac{\int_a^{y_T} [\mu i_c(s,t \mid a,D_t) - \mu i_c(s,t)]\cdot \mathrm{SI}_c(s,t \mid a,D_t)\,\mathrm{d}t}{D_t} \quad \text{(A7)}$$

The measure of years of life lost (YLL) per unit dose is given by

$$\mathrm{YLL}_c(s,a,D_t) = \frac{\int_a^{y_{DT}} S(s,t \mid a)\,\mathrm{d}t - \int_a^{y_T} S_c(s,t \mid a,D_t)\,\mathrm{d}t}{D_t} \quad \text{(A8)}$$

As above, when a relative risk model $\mu_c(s,t \mid a,D_t) = \mu_c(s,t)\cdot[1+\mathrm{ERR}_c(s,a,y,D_t)]$ is assumed, this reduces to:

$$\mathrm{YLL}_c(s,a,D_t) = \frac{\int_a^{y_T} \exp\left[-\int_a^t \mu(s,w)\,\mathrm{d}w\right]\mathrm{d}t - \int_a^{y_T} \exp\left[-\int_a^t \mu(s,w)+\mu_c(s,w)\cdot\mathrm{RR}_c(s,a,w-a,D_t)\,\mathrm{d}w\right]\mathrm{d}t}{D_t} \quad \text{(A9)}$$

This measure has been used by many scientific committees (BEIR V Committee, 1990; ICRP, 1991; UNSCEAR, 1994, 2000) and others (Little et al, 1992, 1997, 1999). A related measure, *years of life lost per radiation-induced cancer* (YLLRIC), which is given by

$$\mathrm{YLLRIC}_c(s,a,D_t) = \frac{\mathrm{YLL}_c(s,a,D_t)}{\mathrm{REID}_c(s,a,D_t)} \quad \text{(A10)}$$

has also been employed by some (BEIR V Committee, 1990; ICRP, 1991; Little et al, 1999; UNSCEAR, 2000).

The non-constancy of all six measures of risk as a function of the test dose, D_t, should be noted, even when the excess relative risk, $\mathrm{ERR}(s,a,t,D_t)$, is linear in D_t; this is a consequence of the non-linearity (in D_t) of the numerators of the above expressions.

In calculation of an overall population risk, suitable averages of all of the above measures have to be taken, averaged over the age-at-exposure distribution in the hypothetical exposed population. Most scientific committees (BEIR V Committee, 1990; ICRP, 1991; UNSCEAR, 1994, 2000) and others (Little et al, 1992, 1997, 1999; Bennett et al, 2004) use the equilibrium population distribution in the absence of radiation exposure, $S_c(s,a) = \exp\left[-\int_0^a \mu(s,w)\,\mathrm{d}w\right]$, and weight across sexes by the relative birth rates of each sex (in most populations approximately equal). Using the equilibrium distribution has the advantage that the time distribution of the administered pattern of dose does not matter: assuming linearity of the excess relative risk $\mathrm{ERR}(s,a,t,D)$ in dose, D, all risk measures are approximately (asymptotically in the low dose limit) invariant to arbitrary fractionation of a given test dose, D_t, over time. In principle, other age and sex distributions could be used to derive aggregate risks – for example, the actual population distribution by age and sex at a given time for some country. However, population risk measures for a population that is not in equilibrium when the radiation dose is given will not be (asymptotically in the low dose limit) invariant to the pattern of test dose distribution.

A1 References

BEIR V Committee (Committee on Biological Effects of Ionizing Radiation) (1990). Health Effects of Exposure to Low Levels of Ionizing Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

Bennett J, Little MP and Richardson S (2004). Flexible dose–response models for Japanese atomic bomb survivor data: Bayesian estimation and prediction of cancer risk. *Radiat Environ Biophys,* **43,** 233–45.

ICRP (1991). 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. *Ann ICRP,* **21**(1–3).

Little MP, Hawkins MM, Charles MW and Hildreth NG (1992). Fitting the Armitage-Doll model to radiation-exposed cohorts and implications for population cancer risks. *Radiat Res,* **132,** 207–21.

Little MP, de Vathaire F, Charles MW, Hawkins MM and Muirhead CR (1997). Variations with time and age in the relative risks of solid cancer incidence after radiation exposure. *J Radiol Prot,* **17,** 159–77.

Little, MP, Weiss HA, Boice JD Jr, Darby SC, Day NE and Muirhead CR (1999). Risks of leukemia in Japanese atomic bomb survivors, in women treated for cervical cancer, and in patients treated for ankylosing spondylitis. *Radiat Res,* **152**(3), 280–92. Erratum in *Radiat Res,* **153**(2), 243 (2000).

Thomas D, Darby S, Fagnani F, Hubert P, Vaeth M and Weiss K (1992). Definition and estimation of lifetime detriment from radiation exposures: principles and methods. *Health Phys,* **63,** 259–72.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1993). Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1994). Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000). Sources and Effects of Ionizing Radiation. Volume II: Effects. UNSCEAR 2000 Report to the General Assembly, with scientific annexes. New York, United Nations.

Appendix B
Issues Relating to Cancer Risk Calculations

B1 Risk models

The risk estimates presented here are based on recent data from the follow-up of the Life Span Study of the survivors of the atomic bombings in Japan. The recent analysis by Preston et al (2004) of Life Span Study mortality data based on mortality follow-up from October 1950 to December 2000 is employed, as well as the latest analysis of the solid cancer incidence data based on follow-up from January 1958 to December 1998 (Preston et al, 2007). All models used are based on those fitted to these data in the UNSCEAR 2006 report (UNSCEAR, 2008). The Life Span Study data that are used employ the recently revised DS02 dosimetry (Young and Kerr, 2005). For some time it was thought that the neutron dose estimates for the survivors of the bombing of Hiroshima using the previous (DS86) dosimetry were systematic underestimates, particularly for survivors from beyond 1000 m from the hypocentre (Roesch, 1987; Straume et al, 1992). This led to substantial multinational efforts to develop a new dose assessment system, the DS02 dosimetry (Cullings and Fujita, 2003; Young and Kerr, 2005). Recent analysis of all the data, including those on fast-neutron activation products, suggests that there are no appreciable systematic errors in the DS86 estimates of neutron doses for survivors of the bombing of Hiroshima (Cullings and Fujita, 2003; Straume et al, 2003; Young and Kerr, 2005). The DS02 dosimetry differs slightly from the DS86 system, for both neutron and gamma doses, by amounts generally of no more than 20% in the range up to 1500 m from the two hypocentres, where survivors received the greatest doses (Cullings and Fujita, 2003; Young and Kerr, 2005). Analyses of the Radiation Effects Research Foundation (RERF) epidemiological data using the new dosimetry indicate that cancer risk estimates might decrease by about 8% as a result, with no appreciable change in the shape of the dose response or in the age and time patterns of excess risk (Preston et al, 2004).

The cancer risk models that are fitted to this dataset for the purposes for deriving population risk estimates were developed specifically for the UNSCEAR 2006 report (UNSCEAR, 2008). Radiation risks are often described by models for cause-specific death rates or 'hazard functions'. The hazard function, $h(a)$, for mortality at age a is defined as the probability of dying in a short interval $[a, a + \delta]$ divided by the probability of surviving up to age a and the length of the interval δ, in the limit that $\delta \to 0$, or more formally, $h(a) = \lim_{\delta \downarrow 0+} \frac{\text{p[time of death} \in [a, a+\delta]]}{\delta \cdot \text{p[time of death} \geq a]}$. Similar definitions for the hazard function can be derived for deaths from some specific cause, or indeed for the occurrence of any specific type of event, eg the occurrence of cancer. Quite often the hazard function, $h(a)$, will depend on variables other than age only – for example, sex s, calendar period y, and exogenous exposures such as a dose of ionising radiation D delivered at age e, so that the hazard function may be written as $h = h(a,y,s,D,e)$.

In modelling the effect of some exposure, in particular that to ionising radiation, it is usual to consider the difference between the instantaneous cancer death rate, or hazard function, when there has been an exposure, namely $h(a,y,s,D,e)$, and what the instantaneous death rate, or hazard function, would have been without that exposure, namely $h_0(a,y,s,e) = h(a,y,s,0,e)$, the 'baseline' hazard function. This difference is the excess absolute risk (EAR):

$$\mathrm{EAR}(a,y,s,D,e) = h(a,y,s,D,e) - h(a,y,s,0,e) \tag{B1}$$

An essential element of such models is the associated model for the baseline hazard function, which is often of a simple parametric form, for example:

$$h_0(a,y,s,e,c) = \exp[\pi_0 \cdot 1_{c=Nagasaki} + \pi_1 \cdot 1_{s=female} + \pi_2 \cdot \ln(a) + \pi_3 \cdot [\ln(a)]^2 + \pi_4 \cdot e] \tag{B2}$$

where c refers to the city of residence at the time of the bombings (Hiroshima or Nagasaki), s is the sex, a is attained age, e is age at exposure, and π_0, π_1, π_2, π_3 and π_4 are the model parameters (which are often determined by fitting to the data).

Another commonly used measure is the excess relative risk (ERR), which is given by the EAR divided by the baseline hazard:

$$\begin{aligned}\mathrm{ERR}(a,y,s,D,e) &= \mathrm{EAR}(a,y,s,D,e) \,/\, h(a,y,s,0,e) \\ &= [h(a,y,s,D,e) - h(a,y,s,0,e)] \,/\, h(a,y,s,0,e)\end{aligned} \tag{B3}$$

As before, an essential element in the specification of such models is the baseline hazard function, $h_0(a,y,s,e)$, which is again often assumed to have a simple parametric form – for example, along the lines of expression B2.

Corresponding to these methods for decomposing the hazard function are two much used models of radiation-induced cancer risk. Until the late 1980s, two fairly simple models for describing radiation-induced cancer risks were used by bodies such as UNSCEAR (1988) and other national and international committees, such as the BEIR III Committee (1980) and ICRP (1991). These are empirical models, which do not depend on assumptions about specific mechanisms of carcinogenesis. The first is the 'time-constant absolute (or additive) risk projection model', which assumes that, after some 'latent period', the annual excess cancer risk is constant. This results in the cancer rate following exposure to a dose D of radiation being given by

$$h_0(a,s) + F(D) \tag{B4}$$

where $h_0(a,s)$ is the baseline cancer hazard function in the absence of exposure to radiation, ie the underlying cancer rate at age a and for sex s. $F(D)$ is the function describing the dose dependency of the cancer risk, which is often of the linear–quadratic form $F(D) = \alpha \cdot D + \beta \cdot D^2$. In the UNSCEAR 1988 report (UNSCEAR, 1988), a model of this form was used for describing the risk of leukaemia. The second model is the 'time-constant relative (or multiplicative) risk projection model', which assumes that, after some latent

period following an exposure to radiation, the annual cancer rate rises in a manner proportional to the underlying annual cancer risk. This results in the cancer rate following exposure to a dose D of radiation being given by

$$h_0(a,s)\cdot[1+F(D)] \tag{B5}$$

where, as before, $F(D)$ is the function determining the dose dependency of the cancer risk, which again is often of the form $F(D)=\alpha\cdot D+\beta\cdot D^2$.

In the UNSCEAR 1988 report (UNSCEAR, 1988), a model of this form (with a linear dose response) was used for modelling solid cancer risks. Until the late 1980s, both models were used for the purposes of estimating cancer risks. Largely as a result of extra years of follow-up of the survivors of the atomic bombings, it became clear that the relative risk model fitted most solid cancer data much better than the absolute risk model. For this reason, the ICRP (1991) and most other scientific committees (eg the BEIR V Committee, 1990) tend to use the relative risk model rather than the absolute risk model for projecting solid cancer risks to the end of life.

While the relative risk model is the most useful for the purpose of modelling cancer risks, it is the absolute risk that is often of most interest to an exposed individual or population. This is readily derived from the calculated relative risk when the baseline risk is known.

It is well known that, for all cancer subtypes (including leukaemia), the ERR diminishes with increasing age at exposure (Little 1993, 2003; UNSCEAR, 2000). For those irradiated in childhood, there is evidence of a reduction in the ERR of solid cancer 25 or more years after exposure (Little et al, 1991, 1997, 1998; Thompson et al, 1994; Pierce et al, 1996). Therefore, even for solid cancers, various factors have to be employed to simulate the ERR. For many solid cancers, a 'generalised excess relative risk model' is commonly used, in which the cancer rate at t years after exposure, for sex s, following exposure at age e to a dose D of radiation is given by

$$h_0(a,s)\cdot[1+F(D)\cdot\varphi(t,e,s)]=h_0(a,s)\cdot[1+\mathrm{ERR}(D,t,e,s)] \tag{B6}$$

where, as before, $h_0(a,s)$ is the baseline cancer rate, $a = (t + e)$ is the age at observation (attained age) of the person and $F(D)$ is the function determining the dose dependency of the cancer risk, which is often of the form $F(D)=\alpha\cdot D+\beta\cdot D^2$. The expression $\varphi(t,e,s)$ describes the adjustment to the ERR, $F(D)$, as a function of time since exposure t, age at exposure e and sex s.

For leukaemia, neither the time-constant EAR model nor the time-constant ERR model fits well. For reasons largely of ease of interpretation, Preston et al (1994) present most of their analyses of the Life Span Study leukaemia incidence dataset using a 'generalised excess absolute risk model', from which the cancer rate t years after exposure, for sex s, following exposure at age e to a dose D of radiation is given by

$$h_0(a,s)+F(D)\cdot\psi(t,e,s)=h_0(a,s)+\mathrm{EAR}(D,t,e,s) \tag{B7}$$

The expression $\psi(t,e,s)$ describes the adjustment to the EAR, $F(D)$, as a function of time since exposure t, age at exposure e and sex s. As above, very frequently a linear–quadratic form, $F(D) = \alpha \cdot D + \beta \cdot D^2$, is assumed for the dose response.

Given appropriate forms of the adjusting or modifying functions $\varphi(t,e,s)$ and $\psi(t,e,s)$ of the relative and absolute risk, respectively, equivalently good fits to the leukaemia incidence dataset were achieved using both generalised ERR and generalised EAR models (Preston et al, 1994). It is to some extent arbitrary as to which of these two models is used. However, models with equivalent fits to the data can yield somewhat different estimates of population cancer risks. The reason for this is that about half the Life Span Study cohort are still alive (Preston et al, 2004), so that population risk estimations made by scientific bodies (BEIR V Committee, 1990; BEIR VII Committee, 2006; ICRP, 1991; UNSCEAR, 1994, 2000) based on this dataset depend crucially on extrapolating the current mortality and incidence follow-up of this group to the end of life. Uncertainties due to risk projection are greatest for solid cancers, because the radiation-associated excess risk as seen by the Life Span Study is still increasing (Preston et al, 2004, 2007). For leukaemia, the excess risk is decreasing over time (Preston et al, 1994), and most models used predict very few radiation-associated leukaemia deaths or cases in the future.

In modelling solid cancer mortality and incidence for the latest follow-up of mortality and incidence of the survivors of the atomic bombings (Preston et al, 2004, 2007), UNSCEAR (2008) used generalised ERR and EAR models. The following generalised ERR model was used, in which the cancer mortality or incidence rate for age a, age at exposure e, city c, sex s and 'true' colon dose D is given by

$$h_0(a,e,c,s) \cdot \left[1 + (\alpha \cdot D + \beta \cdot D^2) \cdot \exp[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln(a-e) + \kappa_3 \cdot \ln(a)]\right] \quad \text{(B8)}$$

This is a generalised ERR model that is linear–quadratic in dose and that incorporates an adjustment to the ERR for sex s, attained age a, and time since exposure $(a - e)$.

The dose to the colon is used to be representative of an average dose to the whole body for the purposes of deriving risks for solid cancers.

A generalised EAR model was also fitted in which the mortality or incidence rate is given by

$$h_0(a,e,c,s) + (\alpha \cdot D + \beta \cdot D^2) \cdot \exp[\kappa_1 \cdot 1_{s=female} + \kappa_2 \cdot \ln(a-e) + \kappa_3 \cdot \ln(a)] \quad \text{(B9)}$$

This is a generalised EAR model that is linear–quadratic in dose, and that incorporates an adjustment to the EAR for sex s, attained age a, and time since exposure $(a - e)$.

B2 Low dose response, fractionation and dose rate effects

As noted above, it has been customary to model the dose–response function $F(D)$ that appears in expressions B4 and B5 in fits to biological (UNSCEAR, 1993) and epidemiological (UNSCEAR, 2000) data by the linear–quadratic expression:

$$F(D) = \alpha \cdot D + \beta \cdot D^2 \tag{B10}$$

While this formulation can be drawn from knowledge of chromosome repair (eg Kellerer and Rossi, 1978), on a more heuristic basis, it represents the second-order Taylor series expansion of the dose response. There is significant curvilinearity in the dose response for leukaemia in the Life Span Study (Pierce and Vaeth, 1991; Preston et al, 1994; Little and Muirhead, 1996, 1998; Little et al, 1999), although for solid cancers, apart from non-melanoma skin cancer (Thompson et al, 1994; Little and Charles, 1997) and bone cancer (Rowland et al, 1978), there has until recently generally been little evidence for anything other than a linear dose–response relationship for the Japanese cohort (Pierce and Vaeth, 1991; Little and Muirhead, 1996, 1998) or for any other group (UNSCEAR, 2000, 2008). However, the most recent follow-up of the survivors of the atomic bombings exhibits a pronounced and statistically significant upward curvature (ie the rate of increase in the risk per unit dose is increasing as the dose increases) in the low dose (less than 2 Sv) region (Preston et al, 2004), as will be discussed at greater length below.

It should be noted that, as well as differences in the effectiveness (per unit dose) relating to the total dose received, there are also possible variations in effectiveness as a result of dose fractionation (ie the splitting of a given dose into a number of smaller doses suitably separated in time) and dose rate (UNSCEAR, 1993). This is not surprising from a radiobiological point of view. If a given dose is administered at progressively lower dose rates (ie giving the same total dose over longer periods of time), or is split into many fractions, the biological system has time to repair the damage, so that the total damage induced will be less (UNSCEAR, 1993). Therefore, although for cancers other than leukaemia there is generally little justification for assuming anything other than a linear dose–response relationship, ie $\beta = 0$ in equation B10, it may nevertheless be justifiable to employ a dose and dose rate effectiveness factor (DDREF) other than one. (The DDREF is the factor by which risks for high dose and high dose rate exposures are divided to obtain risks for low dose and low dose rate exposures.) The ICRP (1991) recommended that a DDREF of two be used together with linear dose–response models for all cancer sites, largely on the basis of observations from various epidemiological datasets. UNSCEAR (1993) recommended that a DDREF of no more than three be used in conjunction with these linear models. The BEIR VII Committee (2006) estimated what it termed an 'Life Span Study DDREF' to be 1.5 (95% CI 1.1, 2.3) on the basis of estimates of curvature derived from data from animal experiments and from the latest Life Span Study solid cancer incidence data. The BEIR VII Committee also conducted a detailed review of the experimental literature, and documented substantial DDREF values that had been found for chromosomal aberrations and cell mutation (for example, at the HPRT locus), and for carcinogenesis in animals (BEIR VII Committee, 2006). DDREF values in excess of two were seen for many cellular systems; most of the animal cancer studies – the experimental endpoint nearest to cancer in humans — yield '[DDREF] estimates on the order of 2 to 6, with most values in the range 4–5' (BEIR VII Committee, 2006).

Another form to represent dose response, perhaps less commonly used, slightly generalises equation B10:

$$F(D) = (\alpha \cdot D + \beta \cdot D^2) \cdot \exp(\gamma \cdot D) \quad \text{(B11)}$$

This has been employed in fits to biological data (UNSCEAR, 1993) and to epidemiological data (Boice et al, 1987; Little and Muirhead, 1996; Little et al, 1999). The $\alpha \cdot D + \beta \cdot D^2$ component represents the effect of (carcinogenic) mutation induction, while the $\exp(\gamma \cdot D)$ term represents the effect of cell sterilisation or killing. In general, the cell-sterilisation coefficient, γ, is less than zero. Essentially this expresses the idea that there is a competing mechanism due to cell killing, which is more effective at higher radiation doses. A dead cell cannot proliferate and become the focus of a malignant clone. Variant forms of the cell-sterilisation term $\exp(\gamma \cdot D)$ that incorporate higher powers of dose D, ie $\exp(\gamma \cdot D^k)$ for $k > 1$, are sometimes employed (UNSCEAR, 1993; Little and Charles, 1997).

Although it is generally assumed that protraction of radiation dose results in a reduction of effect (ie DDREF > 1), largely as a result of the extra time that protraction allows for cellular repair processes to operate, there are biological mechanisms that could increase the effect when dose is protracted (ie DDREF < 1). Bystander effects, whereby cells that are not directly exposed to radiation exhibit adverse biological effects, have been observed in a number of experimental systems *in vitro* and *in vivo* (Morgan, 2003a,b). The bystander effect implies that the dose response after broadbeam irradiation could be highly concave at low doses because of saturation of the bystander effect at high doses. This would mean that linear extrapolation from data for high dose exposures would lead to substantial underestimates of effects at low doses. Brenner et al (2001) proposed a model for the bystander effect based on the oncogenic transformation data of Sawant et al (2001) and Miller et al (1999) for *in vitro* exposure of C3H 10T½ cells to alpha particles. Brenner et al (2001) discussed evidence from experimental systems consistent with concluding that the linear extrapolation of high dose effects to low doses underestimates oncogenic transformation rates by a factor of between 60 and 3000. However, Little and Wakeford (2001) assessed the ratio of the lung cancer risk for persons exposed to low (residential) doses of radon decay products to that for persons (underground miners) exposed to high doses of radon decay products; the ratio lay in the range 2–4 (95% CI <1, ~14). This implies that low dose rate lung cancer risks associated with alpha-particle exposure are not seriously underestimated by extrapolation from the high dose miner data; it also implies that the bystander effect observed in the C3H 10T½ cell system cannot play a large part in the process of lung carcinogenesis in humans due to radon exposure.

As noted above, in the latest follow-up of the survivors of the atomic bombings there has emerged evidence of a statistically significant ($p < 0.05$) upward curvature in the dose response for solid cancer mortality in the low dose range (colon dose less than 2 Sv) (Preston et al, 2004; Walsh et al, 2004), although this is not observed over the full dose range (0–4 Sv). Similar findings have not as yet been observed in the solid cancer incidence data (Thompson et al, 1994, Pierce and Preston, 2000; Preston et al, 2007), so caution is advised in interpretation of this finding. In general, there are only weak indications of curvature in the dose response for particular solid cancer sites in the latest cancer incidence data (Preston et al, 2007), with the possible exception of bone cancer and non-melanoma skin cancer.

Measurement error can substantially alter the shape of the dose–response relationship and hence the derived population risk estimates (Thomas et al, 1993). The problem of dosimetric error for the RERF data has been investigated by Jablon (1971) and Gilbert (1984), and subsequently in a series of papers by Pierce and colleagues (Pierce et al, 1990, 1992, Pierce and Vaeth, 1991) and Little and colleagues (Little and Muirhead, 1996, 1998, 2000; Little et al, 1999; Bennett et al, 2004). Because of the marked effect of adjusting for dosimetric errors on the shape of the dose–response curve, all the analyses presented in this report employ such dosimetric adjustments, using the regression calibration methodology developed by Pierce and colleagues (Pierce et al, 1990, 1992; Pierce and Vaeth, 1991) for the incidence data and the Bayesian methodology developed by Little and colleagues (Little and Muirhead, 1996, 1998, 2000; Little et al, 1999; Bennett et al, 2004) for the mortality data. Jablon (1971) investigated the errors in the dosimetry for the survivors of the atomic bombings and found that the errors were most likely to be log-normally distributed, with a geometric standard deviation (GSD) of about 30%. The analyses of this report employ the 'central' estimate of 35% for the GSD. This is the same central estimate as used by Pierce et al (1990) and assumed by Little and colleagues (Bennett et al, 2004; Little and Muirhead, 1996, 1998, 2000; Little et al, 1999).

B3 Projection methods

In the UNSCEAR 2000 report, some use was made of generalised ERR models for solid cancer incorporating adjustment for attained age and sex, and also such models with adjustment for age at exposure and sex (UNSCEAR, 2000). However, it is clear from the data on solid cancer incidence (Thompson et al, 1994; Little et al, 1997, 1999), as also from the latest data on mortality (Preston et al, 2004), that these models are not optimal. Detailed comparison of models with various sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city) in the latest follow-up of the solid cancer mortality and incidence data (Preston et al, 2004) suggested that, as indicated by the form of model B8 above, the optimal generalised ERR model for many cancer sites was one with adjustment for sex, time since exposure and attained age. Among generalised EAR models for solid cancer mortality and incidence with these sorts of adjustment (all combinations of logarithmic adjustment for attained age, age at exposure, time since exposure, sex and city), as indicated by the form of model B9 above, again the optimal model for many sites was one with adjustment for the time since exposure and attained age. There was little to choose between the fits of these two classes of model (generalised ERR and generalised EAR). The UNSCEAR 2006 report therefore uses both models to project cancer risk over time (UNSCEAR, 2008). The mortality risks for both of these models evaluated using Bayesian Markov Chain Monte Carlo (MCMC) methods are presented in Chapter 4, Tables 4.1–4.3. Table 4.6 presents summary risk values, together with various other recent estimations of population risks for solid cancer mortality.

In the UNSCEAR 2000 report, similar models were employed for projection of the risk of solid cancer incidence as for the risk of mortality due to solid cancer (UNSCEAR, 2000). In particular, generalised ERR models with adjustment for powers of attained age or powers of age at exposure were used in that report. In the UNSCEAR 2006 report, a general framework for risk projection was used for the generalised ERR and EAR models given as expressions B8 and B9 (UNSCEAR, 2008).

As detailed in Appendix A, four measures of population risk relevant to mortality are estimated, namely: excess cancer deaths (ECD), risk of exposure-induced death (REID), years of life lost (YLL) per unit dose, and years of life lost if radiation-induced cancer death occurs (years of life lost per radiation-induced cancer death) (YLLRIC). For cancer incidence, the measure of risk expressed as exposure-induced cancer incidence (REIC) is used. Persons are assumed capable of surviving in principle up to the age of y_T (121 years here), at which point they are assumed to die (ie the population is truncated at that age). It was further assumed that there are no excess solid cancer cases or deaths in the first five years after exposure, and no excess leukaemia deaths in the first two years after exposure. Otherwise the temporal expression of risk, in particular the projection of risk to the end of life, is as predicted by the fitted models given as expressions B8 and B9.

B4 Populations, mortality rates and cancer incidence

Risks are calculated separately for populations having the population structure, mortality rates and cancer incidence of a current UK population. These calculations used mortality rates for England and Wales in 2003 (ONS, 2004a) and cancer incidence rates for England in 2001 (ONS, 2004b). For the purposes of calculating cancer mortality risks, 'solid cancer' is defined to be any cause of death with an International Classification of Diseases 10th revision code (ICD10) of C00–C80 or C97. The populations are assumed to be in equilibrium prior to radiation exposure, an assumption commonly made in such calculations (Bennett et al, 2004; Little et al, 1992, 1997, 1999). All high dose rate risks are generally evaluated using the models given as expressions B8 and B9 fitted to the various Life Span Study mortality and cancer incidence datasets (Preston et al, 2004, 2007). Exceptional sites are cancers of the oesophagus, colon, liver, bone, urinary bladder and brain. For these sites, because of difficulties in obtaining convergence of the fitted Markov chains, models without the adjusting power of time since exposure modifying the radiation dose effect in expressions B8 and B9 were used, equivalent to setting the coefficient $\kappa_2 = 0$. For similar reasons, for the brain cancer EAR model we imposed the additional constraint $\kappa_1 = \kappa_2 = \kappa_3 = 0$. All cancer incidence risks are derived from Bayesian MCMC models fitted using WinBUGS 1.4.3 (Lunn et al, 2000), using chains of length 55,000, the first 20,000 samples of which were discarded (because equilibrium had not been achieved). For all solid cancer (and leukaemia) mortality chains of 100,000 were used, with the first 50,000 discarded, as per the models used in the UNSCEAR 2006 report (UNSCEAR, 2008) and also in Little et al (2008).

The dispersion in the brain and central nervous system cancer ERR model was such that a relatively few elements of the posterior sample predict a very large population cancer risk, resulting in a mean risk much greater than the median. For this reason the median values were preferred for this model and are quoted in Table 4.5 (all the other point estimates in Table 4.5 are mean values).

B5 Transfer of risk estimates between populations

Risks of cancer and cancer mortality were transferred by means appropriate for each of the two sorts of model (generalised ERR and generalised EAR). Therefore, for generalised ERR models (time-, age- and sex-specific), the ERR was assumed to be invariant between populations, whereas for generalised EAR models (time-, age- and sex-specific), the EAR was assumed to be invariant. So, for example, if the age- and sex-specific solid cancer rates for the population being considered are given (from published tabulations, such as ONS, 2004a,b) by $\lambda(a,s)$, then, when using the generalised ERR model B8, the cancer rate following a dose D incurred at age e will be:

$$\lambda(a,s)\cdot\left[1+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot 1_{s=female}+\kappa_2\cdot\ln(a-e)+\kappa_3\cdot\ln(a)]\right] \quad \text{(B12)}$$

whereas if the generalised EAR model B9 is being used, the cancer rate is:

$$\lambda(a,s)+(\alpha\cdot D+\beta\cdot D^2)\cdot\exp[\kappa_1\cdot\ln(a-e)+\kappa_2\cdot\ln(a)] \quad \text{(B13)}$$

where again the underlying cancer or cancer mortality rate $\lambda(a,s)$ is estimated from the published tabulations (ONS, 2004a,b).

B6 References

BEIR III Committee (Committee on Biological Effects of Ionizing Radiation) (1980). The Effects on Populations of Exposure to Low Levels of Ionizing Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR V Committee (Committee on Biological Effects of Ionizing Radiation) (1990). Health Effects of Exposure to Low Levels of Ionizing Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

BEIR VII Committee (Committee to Assess Health Risks from Exposure to Low Levels of Ionising Radiation) (2006). Health Risks from Exposure to Low Levels of Ionising Radiation. US National Academy of Sciences, National Research Council. Washington DC, National Academy Press.

Bennett J, Little MP and Richardson S (2004). Flexible dose-response models for Japanese atomic bomb survivor data: Bayesian estimation and prediction of cancer risk. *Radiat Environ Biophys,* **43,** 233–45.

Boice JD Jr, Blettner M, Kleinerman RA, Stovall M, Moloney WC, Engholm G, et al (1987). Radiation dose and leukemia risk in patients treated for cancer of the cervix. *J Natl Cancer Inst,* **79,**1295–311.

Brenner DJ, Little JB and Sachs RK (2001). The bystander effect in radiation oncogenesis: II. A quantitative model. *Radiat Res,* **155**(3), 402–8.

Cullings HM and Fujita S (2003). The way to DS02: resolving the neutron discrepancy. *RERF Update,* **14**(Part 1), 17–23.

Gilbert ES (1984). Some effects of random dose measurement errors on analyses of atomic bomb survivor data. *Radiat Res,* **98,** 591–605.

ICRP (1991). 1990 Recommendations of the International Commission on Radiological Protection. ICRP Publication 60. *Ann ICRP,* **21**(1–3).

Jablon S (1971). Atomic Bomb Radiation Dose Estimation at ABCC. ABCC TR/23-71. Hiroshima, Atomic Bomb Casualty Commission.

Kellerer AM and Rossi HH (1978). A generalized formulation of dual radiation action. *Radiat Res,* **75,** 471–88.

Little MP (1993). Risks of radiation-induced cancer at high doses and dose rates. *J Radiol Prot,* **13,** 3–25.

Little MP (2003). Risks associated with ionizing radiation. *Br Med Bull,* **68,** 259–75.

Little MP and Charles MW (1997). The risk of non-melanoma skin cancer incidence in the Japanese atomic bomb survivors. *Int J Radiat Biol,* **71,** 589–602.

Little MP and Muirhead CR (1996). Evidence for curvilinearity in the cancer incidence dose–response in the Japanese atomic bomb survivors. *Int J Radiat Biol,* **70,** 83–94.

Little MP and Muirhead CR (1998). Curvature in the cancer mortality dose response in Japanese atomic bomb survivors: absence of evidence of threshold. *Int J Radiat Biol,* **74**(4), 471–80.

Little MP and Muirhead CR (2000). Derivation of low-dose extrapolation factors from analysis of curvature in the cancer incidence dose response in Japanese atomic bomb survivors. *Int J Radiat Biol,* **76,** 939–53.

Little MP and Wakeford R (2001). The bystander effect in C3H 10T½ cells and radon-induced lung cancer. *Radiat Res,* **156,** 695–9.

Little MP, Hawkins MM, Shore RE, Charles MW and Hildreth NG (1991). Time variations in the risk of cancer following irradiation in childhood. *Radiat Res,* **126**(3), 304–16. Erratum in *Radiat Res,* 1992; **132**(1), 126.

Little MP, Hawkins MM, Charles MW and Hildreth NG (1992). Fitting the Armitage-Doll model to radiation-exposed cohorts and implications for population cancer risks. *Radiat Res,* **132,** 207–21.

Little MP, de Vathaire F, Charles MW, Hawkins MM and Muirhead CR (1997). Variations with time and age in the relative risks of solid cancer incidence after radiation exposure. *J Radiol Prot,* **17,** 159–77.

Little MP, de Vathaire F, Charles MW, Hawkins MM and Muirhead CR (1998). Variations with time and age in the risks of solid cancer incidence after radiation exposure in childhood. *Stat Med,* **17,** 1341–55.

Little MP, Muirhead CR and Charles MW (1999). Describing time and age variations in the risk of radiation-induced solid tumour incidence in the Japanese atomic bomb survivors using generalized relative and absolute risk models. *Stat Med,* **18**(1), 17–33.

Little MP, Deltour I and Richardson S (2000). Projection of cancer risks from the Japanese atomic bomb survivors to the England and Wales population taking into account uncertainty in risk parameters. *Radiat Environ Biophys,* **39,** 241–52.

Little MP, Hoel DG, Molitor J, Boice JD, Wakeford R and Muirhead CR (2008). New models for evaluation of radiation-induced lifetime cancer risk and its uncertainty employed in the UNSCEAR 2006 report. *Radiat Res,* **169**(6), 660–76.

Lunn DJ, Thomas A, Best N and Spiegelhalter D (2000). WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput,* **10,** 325–37.

Miller RC, Randers-Pehrson G, Geard CR, Hall EJ and Brenner DJ (1999). The oncogenic transforming potential of the passage of single α particles through mammalian cell nuclei. *Proc Natl Acad Sci USA,* **96,** 19–22.

Morgan WF (2003a). Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects *in vivo,* clastogenic factors and transgenerational effects. *Radiat Res,* **159**(5), 581–96.

Morgan WF (2003b). Non-targeted and delayed effects of exposure to ionizing radiation: I. Radiation-induced genomic instability and bystander effects *in vitro. Radiat Res,* **159**(5), 567–80.

ONS (Office for National Statistics) (2004a). Mortality Statistics Cause. Review of the Registrar General on Deaths by Cause, Sex and Age, in England and Wales, 2003. Series DH2 No. 30. London, Stationery Office.

ONS (Office for National Statistics) (2004b). Cancer Statistics Registrations. Registrations of Cancer Diagnosed in 2001, England. Series MB1 No. 32. London, Stationery Office.

Pierce DA and Preston DL (2000). Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiat Res,* **154**(2), 178–86.

Pierce DA and Vaeth M (1991). The shape of the cancer mortality dose–response curve for the A-bomb survivors. *Radiat Res,* **126**(1), 36–42.

Pierce DA, Stram DO and Vaeth M (1990). Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res,* **123**(3), 275–84.

Pierce DA, Stram DO, Vaeth M, et al (1992). The errors-in-variables problem: considerations provided by radiation dose–response analyses of the A-bomb survivor data. *J Am Stat Assoc,* **87**(418), 351–9.

Pierce DA, Shimizu Y, Preston DL, Vaeth M and Mabuchi K (1996). Studies of the mortality of A-bomb survivors. Report 12, Part 1. Cancer: 1950–1990. *Radiat Res,* **146,** 1–27.

Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, et al (1994). Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat Res,* **137**(2 Suppl), S68–S97. Erratum in *Radiat Res,* **139,** 129.

Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S and Kodama K (2004). Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res,* **162,** 377–89.

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al (2007). Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res,* 168, 1–64.

Roesch WC (ed) (1987). US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Volume 1. Hiroshima, Radiation Effects Research Foundation.

Rowland RE, Stehney AF and Lucas HF Jr (1978). Dose–response relationships for female radium dial workers. *Radiat Res,* **76**(2), 368–83.

Sawant SG, Randers-Pehrson G, Geard CR, Brenner DJ and Hall EJ (2001). The bystander effect in radiation oncogenesis: I. Transformation in C3H 10T½ cells *in vitro* can be initiated in the unirradiated neighbors of irradiated cells. *Radiat Res,* **155,** 397–401.

Straume T, Egbert SD, Woolson WA, Finkel RC, Kubik PW, Gove HE, et al (1992). Neutron discrepancies in the DS86 Hiroshima dosimetry system. *Health Phys,* **63,** 421–6.

Straume T, Rugel G, Marchetti AA, Rühm W, Korschinek G, McAninch JE, et al (2003). Measuring fast neutrons in Hiroshima at distances relevant to atomic-bomb survivors. *Nature,* **424,** 539–42.

Thomas D, Stram D and Dwyer J (1993). Exposure measurement error: influence on exposure-disease. Relationships and methods of correction. *Annu Rev Public Health,* **14,** 69–93.

Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, et al (1994). Cancer incidence in atomic bomb survivors. Part II. Solid tumors, 1958–1987. *Radiat Res,* **137**(Suppl), S17–S67. Erratum in *Radiat Res,* **139,** 129.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1988). Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 1988 Report to the General Assembly, with annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1993). Sources and Effects of Ionizing Radiation. UNSCEAR 1993 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (1994). Sources and Effects of Ionizing Radiation. UNSCEAR 1994 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000). Sources and Effects of Ionizing Radiation. Volume II: Effects. UNSCEAR 2000 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2008). Effects of Ionizing Radiation. UNSCEAR 2006 Report to the General Assembly, with scientific annexes. New York, United Nations.

Walsh L, Rühm W and Kellerer AM (2004). Cancer risk estimates for gamma-rays with regard to organ-specific doses. Part II: site-specific solid cancers. *Radiat Environ Biophys,* **43,** 225–31.

Young RW and Kerr GD (eds) (2005). Report of the Joint US–Japan Working Group. Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki. Hiroshima, Radiation Effects Research Foundation.

Appendix C
Impact of Several Factors on Risk Models

Table C1 demonstrates the difference made by use of the latest DS02 dosimetry, by the choice of risk models and by the period of fit of the risk models. Models were fitted to data corresponding to the period 1950–2000, the full period of follow-up in the current mortality data (Preston et al, 2004), as well as over 1950–1990, corresponding to the period available for the Life Span Study mortality data (Pierce et al, 1996), as was used, for example, in the UNSCEAR 2000 report (UNSCEAR, 2000). For illustrative purposes we consider two linear generalised excess relative risk (ERR) models, one with adjustment to the ERR for age at exposure only (corresponding to one of the models used in the UNSCEAR 2000 report, and the other with adjustment to the ERR for attained age and time since exposure, which we regard as more

TABLE C1 Solid cancer mortality risks for a current (2003) UK population, assuming a test dose, D_t, of 0.1 Sv, using linear generalised ERR models [models described in Table 45 of the UNSCEAR 2006 report (UNSCEAR, 2008) and analogues] fitted using DS86 and DS02 dose estimates, and using follow-up over the periods 1950–1990 and 1950–2000

Risks are calculated for a population in equilibrium (mortality rates and population structure of the current UK population) from linear ERR models fitted to Life Span Study mortality data (Preston et al, 2004), assuming 35% GSD errors

Period of fit	Dose estimates used	Model, modifying terms [a]	Percentage of excess cancer deaths (Sv^{-1})	Percentage of radiation-induced cancer deaths (Sv^{-1})	Years of life lost (Sv^{-1})	Years of life lost per radiation-induced cancer death
1950–1990	DS86	ERR, *D*, sex, age, years SE [b]	7.07	8.48	1.128	13.3
1950–1990	DS86	ERR, *D*, sex, age AE [c]	11.48	13.66	1.659	12.1
1950–1990	DS02	ERR, *D*, sex, age, years SE [b]	6.34	7.60	1.010	13.3
1950–1990	DS02	ERR, *D*, sex, age AE [c]	10.35	12.31	1.496	12.2
1950–2000	DS86	ERR, *D*, sex, age, years SE [b]	6.85	8.25	1.137	13.8
1950–2000	DS86	ERR, *D*, sex, age AE [c]	10.69	12.73	1.539	12.1
1950–2000	DS02	ERR, *D*, sex, age, years SE [b]	6.12	7.36	1.015	13.8
1950–2000	DS02	ERR, *D*, sex, age AE [c]	9.63	11.46	1.387	12.1

Notes

a ERR = generalised excess relative risk, years SE = years since exposure, age AE = age at exposure.

b ERR = $\alpha_s D (a - e)^{\kappa} a^{\tau}$, as per model B8 with quadratic coefficient in dose, β, set to 0 (a = attained age, e = age at exposure, s = sex).

c ERR = $\alpha_s D e^{\kappa}$ (e = age at exposure, s = sex).

nearly optimal for the current follow-up; the form of both models (if not the fitted parameter values) is described in Appendix B.

As can be seen from Table C1, in general use of DS02 versus DS86 dosimetry results in the REID reducing by 9.9–10.8%; for example, for the model with adjustment to ERR for age and year since exposure fitted over 1950–2000 the risk reduces from 8.2% Sv^{-1} with DS86 to 7.4% Sv^{-1} with DS02, a reduction of 10.8%. Changing the interval over which models are fitted (1950–2000 versus 1950–1990) reduces the REID by 2.8–6.9%; for example, for the model with adjustment to the ERR for age and time since exposure using DS02 doses, fitting over 1950–1990 the risk is 7.6% Sv^{-1}, and over 1950–2000 the risk is 7.4% Sv^{-1}, a reduction of 3.1%. The most substantial difference is made by choice of risk model: the newer optimal model, with modification of the ERR by age and time since exposure, generally predicts REID values 35.8–38.3% lower than those predicted by the older model, with adjustment of the ERR for age at exposure only. For example, using DS02 doses and fitting over the period 1950–2000, the REID under the older (age-at-exposure adjusted) model is 11.5% Sv^{-1}, while under the newer (age-, years-since-exposure adjusted) model it is 7.4% Sv^{-1}, a reduction of 35.8%.

C1 References

Pierce DA, Shimizu Y, Preston DL, et al (1996). Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat Res,* **146**(1), 1–27.

Preston DL, Pierce DA, Shimizu Y, et al (2004). Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res,* **162,** 377–89.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2000). Sources and Effects of Ionizing Radiation. Volume II: Effects. UNSCEAR 2000 Report to the General Assembly, with scientific annexes. New York, United Nations.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation) (2008). Effects of Ionizing Radiation. UNSCEAR 2006 Report to the General Assembly, with scientific annexes. New York, United Nations.

Appendix D
Organ Dose Estimates for Medical Radiation Exposure Examples

Dose estimates (mSv) for types of CT scans for adults (for the examples given in Chapter 4)

Organ	Coronary artery calcification CT [a]	CT colonography [b]	Lung CT [c]
Brain	0	0	0
Breast	8	1	4
Stomach	0	13	1
Colon	0	11	0
Liver	0	12	1
Lung	6	3	4
Skin	1	5	1
Thyroid	0	0	1
Bladder	0	12	0
Oesophagus	4	0	4
Red bone marrow	1	6	3
Effective dose (mSv)	**2**	**8**	**1**

Sources

a Kim K-P, Einstein A and Berrington de González A (2009). Coronary artery calcification screening: radiation dose and cancer risk. *Arch Int Med,* **169,** 1188–94.

b Berrington de González A, Kim KP and Yee J (2010). CT colonography: perforation rates and potential radiation risks. *Gastrointest Endosc Clin N Am,* **20**(2), 279–91.

c Berrington de González A, Kim KP and Berg C (2008). Lung CT screening before age 55: radiation risks compared to potential benefits. *J Med Screen,* **15,** 153–8.

Glossary

Absolute risk model	See *additive risk model*.
Additive risk model	A model in which a unit of exposure induces a constant absolute increase in the age-specific disease rate. The increase is usually regarded as independent of, and thus additive to, the background rate and to the increases caused by other exposures.
BEIR	US Committee on the Biological Effects of Ionizing Radiation, which has produced several reports on the effects of exposure to ionising radiation. (*Note:* The BEIR VII Committee was entitled the 'Committee to Assess Health Risks from Exposure to Low Levels of Ionising Radiation'.)
Becquerel	A unit of measurement of radioactive decay. One becquerel represents one radioactive decay per second.
Bias	Error in which estimates differ systematically from the truth. Also known as systematic error.
Case-control study	An investigation into the extent to which a group of persons with a specific disease (the cases) and comparable persons who do not have the disease (the controls) differ with respect to exposure to putative risk factors.
CNS	Central nervous system.
Cohort study	An investigation involving the identification of a group of individuals (the cohort) about whom certain exposure information is collected, and the ascertainment of occurrence of diseases at later times. For each individual, information on prior exposure can be related to subsequent disease experience.
Confidence interval (CI)	An interval that, with a defined level of probability, contains the true value of an unknown parameter. In repetitions of the study, the interval will include the parameter in question on a specified percentage of occasions (eg 90% for a 90% confidence interval).
Confounding factor	A factor that is correlated with both the exposure of interest and disease under investigation.
Dose and dose rate effectiveness factor (DDREF)	A factor applied to risks generated by high dose and dose rate studies when estimating risks to low doses or dose rates to take account of the fact that the dose–response relationship is not linear over a broad range of doses.

Excess absolute risk (EAR)	The absolute difference between the disease rates between two groups of people, eg those exposed to radiation at a given level and those unexposed. An EAR of zero corresponds to neither an increase nor a decrease in risk.
Excess relative risk (ERR)	The relative risk minus one. Thus, an ERR of zero corresponds to a relative risk of one and signifies no raised risk. In instances where the trend in relative risk with dose has been estimated, the change in relative risk per unit dose is often denoted as ERR Gy^{-1} or ERR Sv^{-1}.
Geographical correlation study	Study based on averaging of disease rates and measure(s) of exposure over geographical areas and attempts to correlate them. Particularly susceptible to bias.
gray (Gy)	Unit of ionising radiation dose (joules per kilogram, J kg^{-1}), calculated without weighting of the particular radiation type by its *relative biological effectiveness*.
HCC	Hepatocellular carcinoma. A form of primary liver cancer.
ICD	International Classification of Diseases.
ICRP	International Commission on Radiological Protection.
Life Span Study (LSS)	Cohort study of survivors of the atomic bombings of Hiroshima and Nagasaki, established in October 1950 and followed up for mortality and cancer incidence.
Linear energy transfer (LET)	The rate of loss of energy by a charged particle traversing a material, such as an organ or tissue. Radiations may have a low rate of loss of energy per unit track length and be termed low linear energy transfer, as for X-rays, gamma rays or beta particles; or they may have a high rate of loss of energy and be termed high linear energy transfer (alpha particles and neutrons).
Multiplicative risk model	A model in which a unit of exposure induces a constant relative increase in the disease rate. The increase is therefore independent of the background and of the risks caused by other exposures.
One-sided test	A test for a difference in only one direction (eg a test for an increased – but not a decreased – risk in an exposed group relative to a comparison group).
Person-years (PY)	A unit of measurement combining persons and time, used as denominator in instantaneous incidence and mortality rates. It is the sum of individual years for which the persons in the population have been at risk of developing or dying from the condition of interest.
Precision	The quality of being sharply defined or stated. Provides a measure of the *random error* in an estimate, often expressed using a *confidence interval*.
p (Probability) value	The probability of obtaining a result at least as extreme as that observed in the absence of a raised risk. A result that would arise less than 1 in 20 times in the absence of an underlying effect is often referred to as being 'statistically significant'.

Radiation Effects Research Foundation (RERF)	The binationally (US–Japanese) funded private foundation responsible for performing studies on the survivors of the atomic bombings in Hiroshima and Nagasaki; successor body to the Atomic Bomb Casualty Commission.
Random error	Error that is due to chance and is not completed determined by other factors. Differs from *systematic error*.
Relative biological effectiveness (RBE)	The ratio of the absorbed dose of a reference radiation to the absorbed dose of a given test radiation required to produce the same level of response, all other conditions being kept constant.
Relative risk (RR)	The incidence of disease in an exposed group divided by the incidence of disease in an unexposed group. Usually adjusted for factors such as age and sex.
Relative risk model	See *multiplicative risk model*.
sievert (Sv)	Unit of ionising radiation dose (joules per kilogram, J kg^{-1}), calculated with weighting of the particular radiation type by its *relative biological effectiveness*.
Significance level	See *p (probability) value*.
Standardised incidence ratio (SIR)	The ratio of the observed number of incident cancers in a cohort to that expected in the general population, adjusted for age, sex and calendar period. SIRs are often (but not always) quoted as percentages. For example, an SIR of 100 indicates that the cancer incidence rate in the cohort is the same as that in the general population.
Standardised mortality ratio (SMR)	The ratio of the observed number of deaths from a given cause in a cohort to that expected in the general population, adjusted for age, sex and calendar period. SMRs are often (but not always) quoted as percentages. For example, an SMR of 100 indicates that the mortality rate in the cohort is the same as that in the general population.
Statistical power	The probability that, with a specified degree of confidence, an underlying effect of a given magnitude will be detected in a study.
Synergism	Combined effect of two or more interacting agents that is greater than the sum of the single agent effects with known dose–effect relationships.
Systematic error	See *bias*.
UNSCEAR	United Nations Scientific Committee on the Effects of Atomic Radiation.
UVR	Ultraviolet radiation.
Working Level (WL)	One WL is any combination of short-lived radon decay products in one cubic metre of air that will result in the ultimate emission of 1.3 10^8 MeV of alpha energy.
Working Level Month (WLM)	One WLM is the amount of radiation exposure accumulated during 170 hours at one WL, or 3.5 mJ m^{-3} h.

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