Committee on Medical Aspects of Radiation in the Environment (COMARE)

ELEVENTH REPORT

The distribution of childhood leukaemia and other childhood cancers in Great Britain 1969–1993.

Chairman: Professor A Elliott

Produced by the Health Protection Agency for the
Committee on Medical Aspects of Radiation in the Environment

ISBN 0-85951-578-8

CONTENTS

FOREWORD

i. The aim of this, our Eleventh Report, is to provide an overview of the geographical patterns of variation in the incidence of different types of childhood cancer, and the relation of these to certain socio-demographic factors, and to examine whether spatial or space–time clustering are part of the general pattern of occurrence of childhood leukaemia and other cancers. This report has been written, in response to recommendations in earlier COMARE reports, in order to relate findings around nuclear installations to the general geographical epidemiology of childhood cancer.

ii. There has been much discussion as to whether there is a causal link between radioactivity released from nuclear installations and observed excesses of childhood leukaemia in the areas directly surrounding them. This has been an issue since around 1983 when a possible connection was implicated in a Yorkshire Television documentary entitled *Windscale: The Nuclear Laundry*. As a result of concerns raised by this programme, the Minister of Health set up an Advisory Group chaired by Sir Douglas Black. This Group was commissioned in 1983, to investigate reports of a high incidence of leukaemia in young people living in the village of Seascale, adjacent to the Sellafield nuclear site, and the suggestion that there might be an association between the leukaemia incidence and the radioactive discharges from Sellafield. The report of this Group (Black, 1984) concluded that there was a higher incidence of leukaemia in young people resident in the area, but also concluded that the estimated radiation dose from Sellafield discharges and other sources, received by the local population, could not account for the observed leukaemia incidence on the basis of knowledge available at that time.

iii. The Committee on Medical Aspects of Radiation in the Environment (COMARE) was established in 1985 in response to the final recommendation of the Advisory Group Report (Black, 1984). COMARE's First Report (COMARE, 1986) examined the implications of some further information concerning discharges of uranium oxide particles from Sellafield in the 1950s, which had not been available to the Advisory Group. The Committee concluded that this additional information did not change the essential conclusions of the Black Report.

iv. The findings raised concerns in other areas and, in response, COMARE published its Second Report (COMARE, 1988). This report investigated an apparently similar childhood leukaemia cluster in the town of Thurso near the Dounreay nuclear establishment in the north of Scotland, which again found statistically significant increased levels of leukaemia (Heasman et al*,* 1986a,b).

v. A possible increased leukaemia incidence was also reported among young people living in the vicinity of the Aldermaston Atomic Weapons Research Establishment (AWRE) in Berkshire and the Royal Ordnance Factory (ROF) at Burghfield in North Hampshire (Barton et al*,* 1985; Roman et al*,* 1987). COMARE's Third Report (COMARE, 1989) analysed these reports and

concluded that there was a small but statistically significant increase in registration rates of childhood leukaemia and other childhood cancers in the vicinity of the two sites. It was also noted that around the Atomic Energy Research Establishment (AERE) at Harwell, Berkshire, there was no increase in registration rates of childhood leukaemia.

vi. In COMARE's Third Report, published in 1989, the Committee concluded that the distribution of cases of childhood leukaemia, or other childhood cancer, around individual nuclear installations cannot be seen in a proper context in the absence of comparable information about the general pattern throughout the rest of UK. Of the five recommendations made in the Third Report, two relate to this conclusion. Recommendation 4 stated that '… studies of the geographical distribution of childhood cancer incidence on a nation-wide basis be carried out … thus enabling the patterns found around nuclear sites to be seen in the context of patterns in the rest of the UK'. Recommendation 5 of the Third Report went on to say that '… once the results of the studies outlined in Recommendation 4 are available, this Committee should be asked to participate in a review of the evidence relating to the incidence of childhood cancer around nuclear installations'.

vii. COMARE's Fourth Report (COMARE, 1996) was a review of dosimetric, epidemiological and other scientific data relating to the Sellafield site and the village of Seascale, together with other relevant advances in scientific knowledge, that had become available since the publication in 1984 of the report of the Advisory Group chaired by Sir Douglas Black. COMARE concluded that there was good evidence for a continuing, significantly elevated level of all malignancies in the period covered by the Black Report (1963–1983) and in our subsequent analysis (1984–1992), covering a total period of three decades. A number of other hypotheses involving radiation exposure and also those involving exposures to chemicals and infectious agents, either singly or in combinations, were considered. COMARE concluded that no single factor could account for the excess of leukaemia and non-Hodgkin lymphoma (NHL) but that a mechanism involving infection may be a significant factor affecting the risk of leukaemia and NHL in young people in Seascale.

viii. COMARE's Seventh Report (COMARE, 2002), which reviewed the evidence concerning cancer in the children of parents exposed occupationally to radiation prior to the child's conception, can be found on the COMARE website (www.comare.org.uk).

ix. COMARE's Tenth Report (COMARE, 2005) reviewed the evidence relating to childhood cancers in the vicinity of the major licensed nuclear sites (power stations and other nuclear installations) in Great Britain (www.comare.org.uk). This is also dealt with further in this volume (Chapter 5). There was no evidence of excess numbers of cases in any local 25-km area around any of the nuclear power stations. However, around other nuclear installations the analysis reported an excess of leukaemia and NHL in children near Burghfield, Dounreay and Sellafield; the results were consistent with previously published studies. Aldermaston, Burghfield and Harwell showed a significantly raised incidence of solid tumours in their vicinity. In contrast to a study using similar methods conducted by Sharp et al (1996), a statistically significant increase was seen for the Rosyth Naval Base. However, the finding is thought to be artefactual (COMARE, 2005). COMARE is encouraging the research workers concerned to undertake a detailed comparison of the data and methodologies used – see Recommendation 2 of the Tenth Report.

CHAPTER 1

INTRODUCTION

1.1 The aim of this, our Eleventh Report, is to provide an overview of the geographical patterns of variation in the incidence of different types of childhood cancer, and the relation of these to certain socio-demographic factors, and to examine whether spatial or space–time clustering are part of the general pattern of occurrence of childhood leukaemia and other cancers. This report has been written, in response to recommendations in earlier COMARE reports, in order to relate findings around nuclear installations to the general geographical epidemiology of childhood cancer.

1.2 The Advisory Group chaired by Sir Douglas Black (1984) recommended a series of studies on individuals who had lived near Sellafield. These included a recommendation for a case–control study. A study, led by Professor Martin Gardner, was set up to examine the excess of leukaemia in young people in the vicinity of the plant and to compare the incidence of leukaemia and lymphoma in this population with a control group matched for age and other relevant factors. The study (Gardner et al*,* 1990) centred upon the excess risk of leukaemia in children born in the village of Seascale. It attempted to determine from medical records, population and behavioural data whether this excess could be attributed to any other established risk factors for leukaemia apart from exposure to radiation. The study found no association with factors such as eating locally produced vegetables and seafood and playing on the local beach. However, the study did find a raised risk for children whose fathers worked at the Sellafield plant compared with other local employment groups (interestingly, those with fathers in the iron and steel, chemical and farming occupations also showed comparably increased risk, although of the twelve comparisons involving these groups only one was statistically significant). Another significant finding of this study was that the relative risk decreased rapidly with distance of address of the child from Sellafield, indicating a geographical distribution of risk.

1.3 Various geographical studies have been carried out which have attempted to answer the question of whether there is an increased incidence of childhood leukaemia near nuclear facilities in the UK (Bithell et al*,* 1994; Sharp et al*,* 1996). Studies have also been conducted around particular sites – for example, near the Sellafield plant (Draper et al*,* 1993), the Dounreay facility in Scotland (Black et al*,* 1994), and the Atomic Weapons Establishment at Aldermaston (Roman et al*,* 1987). We have also examined some specific publications from Green Audit covering, for example, areas close to nuclear power stations, such as Oldbury in Gloucestershire (Busby et al*,* 2001). Evidence from a number of other studies has cast doubt on the role played by radiation from such installations in cancer risk (Baron, 1984; Darby and Doll*,* 1987). These studies conclude that the increases in radiation exposure due to the nuclear installations in question are far too small (sometimes by a factor of about 1000, although the size of this factor is a question of some dispute) to account for the increased incidence of certain malignancies that has been reported around some sites. This has given rise to a number of alternative

hypotheses (Ewings et al, 1989; Gardner et al, 1990; Kinlen, 1988). The role of other factors in causing leukaemias in Seascale and possibly Thurso, near Dounreay, has been more closely examined by other more recent studies discussed in depth in our Seventh Report. Population mixing (large-scale mixing of rural and urban populations), possibly leading to exposure of susceptible individuals to infection and local epidemics, has been suggested as a possible cause of the observed clusters of leukaemia cases around nuclear installations. In these areas such mixing involved a large influx of population into a sparsely populated area (Kinlen and Doll, 2004).

1.4 There have also been many studies of the possible existence of 'clusters' of these diseases and, more generally, of geographical variations in incidence. Although early studies such as those by Gardner et al (1990) indicated a link between nuclear facilities and childhood leukaemia, further investigations have found that similar 'clusters' of leukaemia exist in other areas (Alexander et al, 1998; Cartwright et al, 1990).

Structure of the present report

1.5 This report consists of eight chapters. Chapter 2 reviews information on the aetiology of childhood cancer and, in particular, summarises the general evidence for possible mechanisms through which infectious agents can be involved in carcinogenesis.

1.6 Chapters 3 and 4 present a series of new analyses of geographical variations in the incidence of childhood cancer based on data from Great Britain for the 25-year period 1969–1993 (this time period was the most complete validated cancer registration available when we started our analyses). Chapter 3 provides an overview of the geographical patterns of the variation in the incidence of the different types of childhood cancer and describes how these rates vary according to socio-demographic factors. Chapter 4 examines whether childhood cancer shows spatial clustering in certain areas and/or space–time clustering in areas throughout Britain. The diagnostic classification types for childhood cancer used in this report are set out in Table 1.1. The geographical areas on which these analyses are based, together with information on their populations, are set out in Table 1.2.

1.7 Chapter 5 contains a summary of the conclusions from the Tenth Report of COMARE on the incidence of childhood cancer around nuclear installations. Chapter 6 includes a discussion of the results and their relevance to the search for possible causative factors in childhood cancer. The final chapters provide conclusions followed by recommendations.

Table 1.1 Diagnostic classification system for childhood cancers

In this report we use diagnostic groups defined in the International Classification for Childhood Cancer (ICCC) (IARC Technical Report 29, 1996). This system is defined in terms of the site and histological type categories in the International Classification of Disease for Oncology – Second Edition (ICDO-2) (WHO, 1990), and is more relevant for analyses of childhood cancer than the site-based system used for adult cancers. The tables and analyses in this report are based on the twelve main groups defined in the ICCC together with some of the subgroups, as listed below.

Group		**ICCC codes**
1	Total leukaemia	11, 12, 13, 14, 15
2	Lymphomas and reticuloendothelial neoplasms	21, 22, 23, 24, 25
3	Central nervous system and miscellaneous intracranial and intraspinal neoplasms	31, 32, 33, 34, 35, 36
4	Sympathetic nervous system tumours	41, 42
5	Retinoblastoma	51
6	Renal tumours	61, 62, 63
7	Hepatic tumours	71, 72, 73
8	Malignant bone tumours	81, 82, 83, 84, 85
9	Soft-tissue sarcomas	91, 92, 93, 94, 95
10	Germ cell, trophoblastic and other gonadal neoplasms	101, 102, 103, 104, 105
11	Carcinoma and other malignant epithelial neoplasms	111, 112, 113, 114, 115, 116
12	Other and unspecified malignant neoplasms	121, 122
	All neoplasms	All the above
	All neoplasms minus total leukaemia	
Subgroups from the above main groups		
	Lymphoid leukaemia and unspecified leukaemia*	11, 15
	Hodgkin lymphoma	21
	Non-Hodgkin lymphoma	22
	Astrocytoma	32
	Primitive neuroectodermal tumours (PNET)	33
	Retinoblastoma – unilateral	51(part)
	Retinoblastoma – bilateral	51(part)
	Osteosarcoma	81
	Ewing's sarcoma	83

* Cases of leukaemia entered into therapy trials (the majority) have been subject to careful diagnostic review for many years, and thus precise diagnostic sub-classification has been available. It has been less straightforward to obtain precise diagnoses for the other cases of leukaemia in children. Those diagnosed as 'unspecified leukaemia' will in fact be almost entirely acute lymphoblastic leukaemia (ALL). For this reason we have analysed a category of leukaemias described as 'lymphoid and unspecified leukaemia' (LUL). In the dataset used here this subgroup is virtually equivalent to acute lymphoblastic leukaemia and is likely to be more aetiologically homogeneous than Group 1, 'total leukaemia'.

The problem described above has in the past extended to cases of non-Hodgkin lymphoma (NHL). It has been believed that some misclassification existed between LUL and NHL. For this reason, the two have often been combined for analyses in epidemiological studies both in COMARE reports and more generally.

Table 1.2 Number of children aged 0–14 years in specified geographical areas (average population 1969–1993)

England	9,815,987
Wales	591,426
Scotland	1,129,062
Great Britain	11,536,475
English Standard Regions (8)	
North East	665,281
Yorkshire and Humberside	1,049,196
East Midlands	821,225
East Anglia	390,319
South East	3,478,733
South West	866,022
West Midlands	1,134,845
North West	1,410,366
Counties of Great Britain (67)	
6th smallest*	21,609
6th largest*	451,930
Average	172,186
County districts of Great Britain (459)	
6th smallest*	2,662
6th largest*	106,933
Average	25,134
Census wards of Great Britain (10,444)	
6th smallest*	0
6th largest*	7,604
Average†	1,092

* For each of the types of area considered here we have indicated the range of populations, excluding the five smallest and the five largest, ie excluding the most extreme values.

† This average when multiplied by 10,444 (the number of 1981 census wards) does not equal that given above for Great Britain because ward level populations are only available at census years. Consequently, the intermediate years have been interpolated.

CHAPTER 2

AETIOLOGICAL FACTORS IN CHILDHOOD CANCER: REVIEW OF EXISTING INFORMATION

2.1 Much discussion has been devoted to the possible role of infectious agents in the aetiology of childhood leukaemia and possibly other cancers of childhood, in this volume and in the recent scientific literature. Because of this, this chapter is designed to provide a very brief overview of what is generally understood to be known or possible causes of childhood cancers.

2.2 This summary is aimed to direct the reader to recent reviews of this topic and to some more recent publications. Because of the emphasis on the role of infection, Annex 2A is devoted to a more detailed coverage with some consequent overlap with the main text.

Introduction

2.3 Considerable effort has been devoted to discovering the causes of childhood cancers over the last 50 years. Despite extensive investigations, the aetiology of most types of childhood cancer are generally unknown. There are, however, a number of exceptions where specific causes are known or inferred.

2.4 Research into such circumstances has been devoted to investigating pathogenic mechanisms and epidemiology in situations including familial syndromes, unusual environmental events such as the ingestion of particular therapeutic agents in pregnancy or rare instances of population mixing. The aims of these investigations, in part, have been to uncover insights which might be applicable to the generality of the causes of that particular childhood cancer.

2.5 In contrast to this approach, other studies have attempted to address issues which are more likely to be directly applicable to many more cases because the putative exposures in question are part of our common environment. In this category would lie investigations into possible harmful effects of neonatal vitamin K use and searches for viruses (see Annex 2A).

2.6 Investigation into both rare events and common exposures has largely been unproductive with the possible exception of issues relating to population mixing and infections. These investigations have been largely directed to childhood leukaemias and lymphomas (see Annex 2A).

2.7 It is generally accepted that the creation of leukaemic cells depends on two sequential molecular events. This is known as the ‘two-hit’ hypotheses. The first event is regarded as an initiation process, whilst the second events are ‘promotional’. The issue for the childhood leukaemias is when these two events take place. Molecular evidence from comparison of Guthrie blood spots (taken from babies within a few days of birth) and subsequent leukaemic cells now shows conclusively that the first ‘hit’ in childhood acute lymphoblastic leukaemia (ALL) often (possibly always) occurs *in utero* (Wiemels et al, 1999; Greaves and Wiemels, 2003). Postnatal activity of any other causative agent such as infection will thus be in the context of an already existing pre-leukaemic clone. It is not known whether this (*in utero*) genetic lesion is ‘caused’ by either genetic or environmental factors or is a purely random event associated with the natural process of immune system development.

2.8 This report focuses on location at diagnosis and, by implication, environmental factors in that location hence the focus for childhood ALL will be the second 'hit'. Unfortunately there is less information regarding the timing of the two (or more) pathogenic events required for the aetiology of most other childhood cancers.

2.9 It is beyond the scope of this chapter to provide a truly complete overview of known, possible or even unlikely causes of childhood cancer and the reader is referred to several publications which comprehensively and systematically review these investigations up to about 1997 (Little, 1999) and more recently (Stiller, 2004a) or more specifically deal with genetic aspects (Stiller, 2004b), childhood brain tumours (Baldwin and Preston-Martin, 2004) and infectious aetiologies (McNally and Eden, 2004).

2.10 The aim of this chapter is to overview this work briefly and where possible refer the reader to reviews or more recent publications. Annex 2A provides more details regarding issues about infections and surrogates for infectivity, to assist with some of the observations presented in this volume.

Major aetiological factors investigated with respect to childhood cancer

Ionising radiation exposure

2.11 Classically, Stewart et al (1958) showed that X-rays in pregnancy may have caused as much as 5% of all childhood malignancies. Changes in medical technology and practices have substantially reduced antenatal radiation dose and so this is no longer the case. However, the therapeutic use of irradiation can lead to cancers occurring in the treatment volume (see, for example, Ron et al, 1995). It has also been shown that those children exposed within a 150 km radius to fallout from the Chernobyl accident have excesses of thyroid cancer (Shibata et al, 2001).

2.12 Issues of risk related to proximity to nuclear installations are dealt with most recently in COMARE's Tenth Report (COMARE, 2005), which is summarised in Chapter 5.

2.13 Studies of residential exposures to radon gas show little or no risk to the average household (Laurier et al, 2001; UKCCS Investigators, 2002).

Non-ionising radiation exposure

2.14 Ultraviolet light exposures appear unlikely to be linked to an increased risk of retinoblastoma (Jemal et al, 2000). Residential exposure to extremely low frequency electromagnetic fields has been associated with childhood leukaemia at very high levels of exposure, above 0.4 microtesla (Ahlbom et al, 2000). Little research has been conducted on domestic electric fields and the risk of childhood cancer, but so far there are no positive findings (Skinner et al, 2002).

Infectious agents: non-specific

2.15 Non-specific infectious agents are thought to play a role in the aetiology of leukaemias. Briefly, the major underpinning concepts are those of Greaves (1988, 1997) and Kinlen (1988) – see Annex 2A for further information. Greaves has argued that exposure to infectious agents and other immune challenges in early life are necessary for the natural priming of the developing immune system; delay in this may predispose to the development of leukaemia when children are exposed to subsequent infection. Thus Greaves hypothesises that these events can have effects in different directions when exposure occurs at different critical times: with exposure in the first year being protective, whilst exposure in later life can precipitate leukaemia. By contrast, Kinlen has focused on the effect of infectious agents in situations where human populations, which have been isolated, are subsequently exposed to population mixing. He suggests an effect of one or a small number of agents of infection which could, though rarely, lead to leukaemia.

2.16 As well as leading to further biological investigations, these hypotheses have prompted epidemiological investigations into lifestyle aspects of ALL cases and their parents which have been contrasted with those of the general population. The investigations are not for specific viruses (see Annex 2A) but for differences in the immune histories of cases. These studies show that children with ALL have fewer immunisations (Schüz et al, 1999) and in one specific study some vaccinations appear to be protective (Auvinen et al, 2000).

2.17 The hypotheses of Greaves and Kinlen are dealt with in more detail in Annex 2A, together with supporting evidence available from epidemiological and laboratory studies.

Infectious agents: specific viruses

2.18 The Epstein-Barr virus (EBV) is believed to be causally associated with Burkitt's lymphoma in areas of endemic malaria, and with nasopharyngeal carcinoma in other parts of the world (Parkin et al, 1999), conditions mainly affecting adults.

2.19 EBV viral DNA has been found in the tumour cells of a minority (33%) of cases of Hodgkin lymphoma (HL) in children and adults. The demonstration of clonality and the expression of specific viral proteins provide strong arguments that EBV is causal in these cases. The proportion of cases with EBV present in this way is age-at-diagnosis dependent with higher proportions in young children (less than 10 years) and in older adults (over 50 years) (Alexander et al, 2003; Jarrett, 2003). Other epidemiological evidence suggests that HL in young children (and some older persons) is associated with early first exposure to infection.

2.20 Chronic effects of HIV infection and AIDS increase the risk of Burkitt's lymphoma, Kaposi sarcoma, certain non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL) and leiomyosarcomas in children and adults. For Kaposi sarcoma, infection with the herpes virus, HHV8, is also necessary. In children, at least, these occur mostly in developing countries.

2.21 Some small studies of specific tumour DNA of ALL cases have shown that no herpes virus can cause ALL by any direct mechanism. Similar, but technically more complex studies have made it unlikely that any virus causes ALL in this way. See Annex 2A for further details.

Therapeutic drugs

2.22 The, now past, use of the therapeutic agent diethylstilboestrol in pregnancy was associated with the development of clear cell adenocarcinoma of the vagina in older girls (Giusti et al, 1995). There are equivocal reports that the use of phenytoin, an anti-epileptic drug, in pregnancy gives a risk of neuroblastoma in children (Olsen et al, 1990). Chloramphenicol used as an antibiotic in children may result in a leukaemia risk (Shu et al, 1988), whilst the chemotherapeutic agent chlorambucil gives a risk of acute myeloid leukaemia (AML) to children treated for juvenile rheumatoid arthritis (Kauppi et al, 1996). This topic is reviewed by Little (1999). There is little evidence for any harmful effect of intramuscular vitamin K given routinely at birth (Roman et al, 2002).

Environmental chemicals

2.23 No clear links have been shown between environmental pesticide exposure and childhood cancer risk despite numerous studies in this area (Zahm and Ward, 1998; Flower et al, 2004; Reynolds et al, 2005). The association between N-nitroso compound exposures (including tobacco use) by parents and childhood cancer development is generally unconvincing (Boffetta et al, 2000; Pang et al, 2003). However, a recent prospective study from Sweden suggests that a small risk might exist for childhood brain tumours in

those whose mothers smoked in pregnancy (Brooks et al, 2004), whilst a large case–control study suggests paternal exposure to polycyclic aromatic hydrocarbon exposures (including cigarette smoking) might also produce a modest risk of childhood brain tumours (Cordier et al, 2004). No link was found for maternal residence in high traffic density areas and childhood cancer risk (Reynolds et al, 2004).

2.24 The occupations of parents and the risk of cancer in their offspring have been widely researched but few consistent positive associations are documented. Comprehensive reviews of the topic (Colt and Blair, 1998; Little, 1999) describe difficulties in interpretation of data from small studies with poor exposure assessment. A recent report failed to identify any risks for any type of childhood cancer and parental occupation (McKinney et al, 2003a). Ewing's sarcoma has been associated with parental exposure to wood dust (Moore et al, 2005).

2.25 Little work has been carried out on possible links between diet and the risk of childhood leukaemia. However, one study on a wide population of California, USA (Kwan et al, 2004), suggests that consumption of fruit and juices containing vitamin C may confer protective benefits. No association was recorded between an increase in leukaemia and the consumption of hot dogs or lunchmeat.

2.26 A meta-analysis of seven published studies on the consumption of cured meats in pregnancy and its association with childhood brain tumours provides some support for a weak link, particularly with maternal consumption of hot dogs (Huncharek and Kupelnick, 2004).

2.27 Recent ecological studies by Knox (2005a,b, 2006) suggest that there is an increased risk among children exposed in the prenatal or early postnatal period to certain environmental pollutants. Some of the results are very striking but the complexities of the analytical methods and the lack of detailed information to support the methodology make these results uninterpretable.

Inherited aspects

2.28 There are several rare familial diseases, which increase the risk of childhood cancers in affected families. These include the Li-Fraumeni syndrome, caused by germ-line mutations in the TP53 gene, characterised by early onset breast cancer, leukaemia, other childhood cancers and adreno-cortex carcinoma (Varley et al, 1997). They also included Down syndrome, which is linked to the development of childhood leukaemia (Hasle, 2001) and type 1 and 2 neurofibromatosis linked to CNS tumours. Parental consanguinity also appears to increase the risk of childhood cancer (Narod et al, 1997).

2.29 In addition, it has been suggested that subtle variation in a person's genetic make-up may be able to modify an individual's risk of certain diseases by influencing the effects of environmental factors. This type of genetic variation (genetic polymorphisms) is common, occurring (by definition) with a frequency of 1% or more, in many genes, in the general population. The effect of this polymorphic variation is small for most of the gene sites, although there are some notable exceptions, eg the protective link between unusual haemoglobin subtypes and the risk of malaria. An example relating to polymorphisms of apparently small effect might be the risk of childhood leukaemia associated with variant forms of the genes that code for enzymes that are responsible for the metabolism of environmental agents. Results of studies on this effect ranged from no effect to three times higher risk than that associated with the common genetic forms (Garte et al, 2000; Krajinovic et al, 2002; Balta et al, 2003; Yuan et al, 2003). Large studies are typically needed to

investigate gene–disease associations and particularly to investigate how genetic variants modify the effect both of environmental factors and of other genes. Real progress has yet to be made in this area.

2.30 HLA haplotypes, which are part of the gene complex that is linked to an individual's ability to mount an immune response and are involved in susceptibilities to infections, have different patterns in ALL children compared with unaffected persons (Taylor et al, 1998, 2002). These studies compared class II HLA types (DPB1) in cases of leukaemia with solid tumour controls and with cord blood controls (taken from newborn children). Significant differences emerged in both comparisons; the HLA-DPB1 types that predominated in the ALL (and common ALL) cases were those which are already frequent in the UK population.

2.31 These differences in polymorphic variants of an immune function gene are supportive of an infectious component to the aetiology of ALL, and specifically common ALL. That risk is increased in carriers of favourable (ie common) types suggests that a strong immune response (such as would generate proliferative stress) rather than impaired immune response is associated with leukaemia.

2.32 Little is known of similar genetic systems in other childhood cancers.

Summary

2.33 The rare factors, which cause childhood cancer, such as specific genetic syndromes, are unlikely to be dependent on geographical or socio-economic factors.

2.34 The exception to this could be the influences that infectious agents might exert either in the 'non-specific' fashion envisaged by Greaves or from more specific, but unknown, infectious agents as proposed by Kinlen.

2.35 Variation in exposure to physical or chemical environmental agents may explain geographical patterns of incidence of different childhood cancers. Evidence to support this is generally weak, apart from the possible influence of infections on childhood leukaemia (see Annex 2A).

ANNEX 2A

INFECTION, VIRUSES AND RELATED LIFESTYLE FACTORS

Relevant aspects of the descriptive epidemiology of childhood leukaemia

2A.1 The incidence peak in early childhood (1–4 years or 1–7 years) was first observed in the UK (Court-Brown et al, 1960); it was then noted in white people in the USA, then in black people in the USA and, later, in Japan. It is now evident worldwide associated with socio-economic development (Little, 1999) and with community isolation (Alexander et al, 1990), but not ethnicity, although McKinney et al (2003b) noted occurrences of the peak of age 5–9 years in south-Asian children compared to the non-south-Asian population in the UK.

2A.2 It is now known that this peak is attributable to ALL and, indeed, to one immunophenotype subgroup (common ALL) (Greaves and Alexander, 1993).

2A.3 A number of well-defined clusters of childhood leukaemia have been identified; the cause of none has been established. Key examples include Seascale in Cumbria (UK), Niles, Illinois, in the USA (Heath and Hasterlik 1963), Niles, Michigan, in the USA (Heath 2005), and Fallon, Nevada, in the USA (Kinlen and Doll, 2004; Steinmaus et al, 2004). Other than Cumbria, these sights are unrelated to nuclear facilities.

2A.4 In addition, childhood leukaemia shows a general tendency to cluster; that is, the incidence pattern displays localised variation which cannot be explained in terms of larger scale variability (Alexander et al, 1998).

2A.5 The epidemiological evidence for infection as a role in the aetiology of childhood leukaemia has recently been reviewed (McNally and Eden, 2004).

Mechanisms involved in infectious aetiologies of other cancers

2A.6 There are two general mechanisms: direct action of a transforming virus and indirect action of a virus or bacterium which may involve proliferative stress, molecular mimicry or stromal infection or other unknown actions (Greaves and Alexander, 1993).

2A.7 Most of the examples relating to specific viruses are of the first type of mechanism (the animal leukaemic retroviruses – FLV and BLV – and the human retrovirus HTLV1, the herpes viruses EBV and HHV8, and hepatitis viruses) (Beral et al, 1999).

2A.8 However, indirect mechanisms are also established: the bacterium helicobacter pylori is linked with adult gastric lymphoma, and HIV with Kaposi's sarcoma. It is thus plausible that similar mechanisms could contribute to the development of childhood cancers, especially leukaemias and lymphomas.

2A.9 Molecular biology will identify viral DNA in tumour cells only if the direct mechanism applies. Identification of causation under the various possible indirect mechanisms is more difficult.

Specific hypotheses

Kinlen and population mixing

2A.10 Considering the Seascale cluster, Kinlen (1988) proposed that childhood leukaemia is a rare response to a common, but unidentified, infection. Excess cases of the unusual complication, childhood leukaemia, would be likely to occur when large numbers of 'susceptible' and 'infected' children come into contact, as when rural populations mix with urban populations on a large scale, leading to localised epidemics of the (probably subclinical) underlying infection. This was proposed as an explanation for the cluster of childhood leukaemia in Seascale – though it would also explain those in Niles, Illinois, and Fallon, Nevada, USA – all of which experienced major population influxes at the relevant times. Kinlen has proposed that some specific agent(s) is most likely to be involved. Kinlen's hypothesis is not specific regarding the leukaemia subtype or the ages affected. It has been supported by a number of studies designed to test it (Kinlen, 1995; Stiller and Boyle, 1996; Dickinson and Parker, 1999).

Greaves and the hygiene hypothesis

2A.11 Greaves' hypothesis (1988, 1997) grew out of consideration of the childhood peak of ALL and its epidemiological correlates and has been modified to take into account the molecular biology of ALL. In its present form it proposes that immunological isolation (lack of exposure to infection, and/or lack of vaccination) of infants (under 1 year) increases the risk of ALL through, primarily, impaired priming of the developing immune system and, secondly, lack of early exposure to agents for which first exposure occurring later can have pathological sequelae. Under this hypothesis, increased subsequent exposure to infectious agents is predicted to facilitate the development of overt leukaemia. Greaves predicted that both the early and the later effect of infection would also be indirect, ie the agents would indirectly facilitate neoplastic change.

Smith and in utero exposure

2A.12 Smith (Smith et al*,* 1997, 1998) proposed an alternative explanation of the childhood peak and its socio-economic correlates. He suggests that exposure *in utero* (because mothers in developed countries are likely to be more often unexposed) to one or more infectious agents is a cause of childhood ALL. He appears (1997) to favour a direct mechanism and suggests the consequent changes occur *in utero*.

Epidemiological evidence (childhood leukaemias)

Population mixing in areas previously isolated

2A.13 The first test of Kinlen's hypothesis (which cited childhood leukaemia data for the Scottish New Town of Glenrothes) was positive – and identified a 'cluster' which had passed unnoticed. Subsequent work, reviewed in Little (1999) and in a meta-analysis (Kinlen, 1995), has confirmed that this unusual demographical situation is associated with roughly a doubling of incidence of childhood leukaemia (ages 0–14 years). The ages of the cases involved and the leukaemia subtypes vary between studies.

Associations with quantitative measures of population mixing

2A.14 These studies examine the whole of a large geographical area and derive a measure of population mixing in that area. They then test for associations between this measure and incidence of childhood leukaemia and/or ALL. This is entirely distinct from the purpose of Kinlen's studies in which attention is restricted to areas that are initially isolated.

2A.15 Four studies have been conducted of this type for childhood leukaemia (Stiller and Boyle, 1996; Dickinson and Parker, 1999; Law et al*,* 2003; Wartenberg et al, 2004). All but Law et al found increased mixing to be associated with higher incidence of leukaemia (or of ALL) – with statistical significance attained; the mixing is measured at the time of diagnosis (approximately, since census data are used) and at the time of birth (again approximately). Law et al found a significant association in the opposite direction, once again using census data to approximate the demographical

surroundings at the time of diagnosis. Both Law et al and Wartenberg et al also examined other cancers with negative results.

2A.16 These studies use all available case and population data and are free from the effects of response bias which confronts case–control studies; however, they have one critical methodological problem. They must use routine census data which are collected at, usually, ten-year intervals. To quantify the environment for an individual child at the time of diagnosis it is necessary to take the nearest census year; a similar approach is required for the time of birth. The result of these time differences is to dilute any potential effects in the resultant analyses.

Immunological isolation

2A.17 Studies using routine data cannot address this issue because the information required is not normally collected, and since rates of childhood leukaemia are too low for most cohort studies, most analyses have been based on case–control studies. These cannot directly quantify exposure to infection in the first year of life. An alternative is to use proxies: numbers of reported infectious illnesses and social contacts. Evidence from epidemiological studies of childhood atopic illness (Rosenbaum et al, 2005) suggests that the latter is most reliable; this is not surprising since infectious exposures are commonly subclinical.

2A.18 Three studies (Dockerty et al*,* 1999; Chan et al*,* 2002; Gilham et al, 2005) have compared some social contact in the first year of life with none and found a significantly reduced risk of leukaemia in children who had had some social contact. Several others have used day-care (not always restricted to the first year) as a proxy and the majority have reported reduced risk in 'exposed' children (Petridou et al, 1993; Infante-Rivard et al, 2000; Gilham et al, 2005), but one large study (Neglia et al*,* 2000) found no association.

2A.19 Numbers of infectious illnesses have been compared in cases and controls in a small number of studies; van Steensel-Mol et al (1986) and Chan et al (2002) reported a reduced risk of leukaemia for children with more infectious illnesses in the first year of life, but the Inter-Regional Epidemiological Study of Childhood Cancer (IRESCC) (McKinney et al, 1987) found an association in the opposite direction for the first six months of life.

2A.20 Birth order is the only proxy available to studies using routine data and the largest studies demonstrate a clear increased risk for early births within sibships order (Westergaard et al*,* 1997; Dockerty et al, 2001). Other interpretations, however, are available for this increased risk, in addition to immunological isolation, and the literature contains many studies which report no association of risk with birth order.

2A.21 Vaccinations in the first year have been analysed in several case–control studies with moderately consistent evidence that, in general, they reduce risk of subsequent leukaemia; the most consistent evidence is found for conjugate Hib vaccination (Groves et al*,* 1999; Auvinen et al*,* 2000; Ma et al, 2005) – these newer vaccines are administered to children a few months old in contrast to the original Hib vaccine given at two years.

2A.22 Prolonged breastfeeding is likely to have beneficial effects on the developing infant immune system similar to exposure to infections and vaccination. Several epidemiological studies (UKCCS Investigators, 2001) have shown that breastfeeding continued beyond the age of six months is protective against subsequent leukaemia (or the generality of childhood cancer).

2A.23 A study from New York State suggests that the presence of allergies reduces the risk of childhood ALL (Rosenbaum et al, 2005) but overall this study provides little support for delayed infections increasing ALL risk.

Interaction between immunological isolation and delayed exposure

2A.24 Studies of population mixing in areas previously isolated support the belief that these two factors together convey the highest risk of leukaemia. Note, however, that the times at which the area was isolated and mixed need not correspond to infancy and diagnosis for an individual child.

2A.25 Two case–control studies have examined interaction and/or computed results in each time period adjusted for corresponding evidence in the other (Infante-Rivard et al*,* 2000; Chan et al*,* 2002). Both have shown stronger (and significant) evidence of benefit from reduced opportunity for social contacts at the time of diagnosis and increased opportunity during infancy.

2A.26 This positive evidence is consistent with, and offers support for, Greaves' hypothesis but is also consistent with leukaemia being associated with delayed exposure to a leukaemogenic virus.

Specific infectious agents

2A.27 Increased *in utero* exposure to varicella zoster has been reported in cases in a few studies (reviewed in Alexander, 1993). Decreased infant conjunctivitis (McKinney et al*,* 1999), roseola (Chan et al*,* 2002) and otitis media (Neglia et al*,* 2000) in cases have also been reported. Increased tonsillitis in the year before diagnosis was reported in one study (Chan et al*,* 2002).

2A.28 Correlation between national mycoplasma pneumonia infection rates during infancy (low rates), the year before diagnosis (high rates) and ALL rates was shown in one study (Alexander, 1997). Coincidence of a small peak of common ALL in the years after winters in which influenza was judged epidemic in the UK has been noted (Kroll et al, 2006).

Clustering

2A.29 The largest study of spatial clustering of childhood leukaemia (EUROCLUS) records information from across Europe. Many countries reported a generalised small-scale heterogeneity of rates in small areas (Alexander et al, 1998). However, these were rare events which were consistent with the contrasting results from previous studies (reviewed in Little, 1999).

2A.30 This study showed that clustering was strongest for ALL and for the age range 1–4 years but included other age groups and AML.

2A.31 There is a long history of investigations of space–time clustering of childhood leukaemia (reviewed in Little, 1999), often controversial due in part to the adopted method of analyses. Recent analyses have created improved methodologies and used larger datasets. The more recent method of Diggle et al (1995) overcomes problems of arbitrariness. Studies of leukaemia using this methodology are reviewed in McNally and Eden (2004). This topic is also addressed in this report (see Chapter 4).

Seasonality of leukaemias and other childhood cancers

2A.32 Seasonality of the time of birth or diagnosis provides evidence consistent with, and somewhat supportive of, an infectious aetiology. However, seasonality of the time of diagnosis and/or onset of symptoms may instead be attributed to seasonality of independent diagnoses which serve to disclose the incipient cancer. Thus caution is required in interpreting these studies.

2A.33 Seasonality of birth or diagnosis/onset of symptoms has been studied in a small number of large studies, most notably Higgins et al (2001) (all UK diagnoses of leukaemia in a similar time period to that of our data, analysing

times of both birth and diagnosis) and Ross et al (1999) (US Surveillance Epidemiology and End Results (SEER) data – all childhood cancers, analysing times of diagnosis alone). The results of the former were almost entirely negative except for diagnoses or births before 1960. The US study showed significant seasonality of a number of diagnoses: ALL, AML, HL, rhabdomyosarcoma, neuroblastoma, retinoblastoma, osteosarcoma, Wilms' tumour, Ewing's sarcoma, hepatoblastoma and CNS tumours but not NHL. When analyses were restricted to latitudes less than 40 degrees, only CNS tumours showed a seasonal pattern.

2A.34 There is the possibility that the seasonality of any infectious disease causally related to leukaemia or other childhood cancer may show geographical and/or temporal variation. This is to some extent supported by the results of Higgins et al (2001) and Feltbower et al (2001), the latter of which reported different seasonal patterns for childhood leukaemia in two regions of Northern England – both were statistically significant and by positive studies from localised registries (Westerbeek et al, 1998, for dates of diagnosis for common ALL and HL; McNally et al, 2002a, for certain CNS tumours).

Epidemiological evidence (other childhood cancers)

Clustering

2A.35 Over a number a years, there have been a number of investigations of clustering of childhood cancers, other than leukaemia. The majority of these studies have been concerned with space–time clustering, with only a few examining spatial clustering. Most reports have involved only small numbers of cases and have used older methodologies (reviewed in Little, 1999). More recently, studies from North West England have found space–time clustering for CNS tumours (particularly astrocytoma), based on time and place of diagnosis (McNally et al, 2002a); for certain CNS tumours (particularly pilocytic astrocytoma and ependymoma), based on time and place of birth (McNally et al, 2002a); and for Wilms' tumour and soft-tissue sarcoma, also based on time and place of birth (McNally et al, 2003a). There was no space–time clustering for other solid tumours from North West England (McNally et al, 2003a, 2004). One study also from North West England has found weak evidence for spatial clustering of Wilms' tumour (McNally et al, 2003b).

Other evidence: CNS tumours

2A.36 Gilham et al (2005) provide support for some beneficial effect for CNS tumours from early priming of the infant immune system.

Laboratory-based evidence

Serological studies

2A.37 Use of serology in serum banks collected after diagnosis (eg in case–control studies) is of limited value because the disease process itself may lead to the presence of antibodies as much as the prior infection led to the disease.

2A.38 One study (Lehtinen et al, 2003) has used maternal serum collected at antenatal examinations and stored for subsequent analysis. This study found more frequent evidence of EBV reactivation during leukaemia case pregnancies than the controls. The interpretation could possibly be in terms of fetal exposure to EBV and immediate DNA changes; alternatively, postnatal immune control of EBV, and perhaps other herpes viruses, could be impaired with pathological consequences. In addition, the affected cases in this study are focused in those diagnosed under one year; in such cases MLL gene damage is common and it was suggested by the authors that there could be a link between EBV reactivation and the MLL gene rearrangement. Evidence against fetal infection at birth with EBV in cases of childhood leukaemia favours an interpretation of this type (Bogdanovic et al, 2004).

2A.39 A second study of similar design (Lehtinen et al, 2005) has compared maternal infections due to specific bacteria during the pregnancies of cases and

controls and found evidence of statistical significance for associations with helicobacter pylori and of borderline significance for mycoplasma pneumonia. The interpretation is unclear due to the unique nature of these results.

Presence and absence of viral DNA

2A.40 Methodology is now available to screen tumour cells for DNA of specific viruses and for non-specific herpes viruses. In addition, RDA (representational deletion analysis) can compare host and tumour DNA to identify any virus present only in the tumour cells.

2A.41 In searches for specific viral involvement, convincing negative results have been reported for polyoma viruses (Smith et al, 1999; Priftakiis et al, 2003) and for non-specific herpes viruses (MacKenzie et al, 2001).

2A.42 RDA has been conducted by one laboratory with negative results for common ALL (Jarrett, LRF Virus Centre, University of Glasgow, personal communication); this methodology used only a small number of cases but sufficient numbers of replications to have high power of detecting viruses of the size of a retrovirus or larger. It is, therefore, very unlikely that all cases of common ALL contain viral DNA.

CHAPTER 3

INCIDENCE OF CHILDHOOD LEUKAEMIA AND OTHER CHILDHOOD CANCERS IN GREAT BRITAIN: SOME SOCIO-DEMOGRAPHIC FACTORS AFFECTING RATES ANALYSED AT COUNTY DISTRICT AND CENSUS WARD LEVEL

Introduction

3.1 Childhood cancer, usually defined to be cancer occurring in the first 15 years of life, is a rare disease affecting about one child in five- or six-hundred in Great Britain. About one-third of these cases are leukaemia. There has been much media and academic interest in reports of apparent 'clusters' of childhood cancer cases, most frequently leukaemia, or increased incidence rates, particularly in relation to nuclear installations. In this chapter we summarise a series of descriptive and analytical studies of geographical patterns in the incidence of childhood cancers in Great Britain carried out by the Childhood Cancer Research Group (CCRG). An earlier series of analyses was published by the Office of Population Censuses and Surveys (OPCS) (Draper, 1991); the present study is a continuation and expansion of that work, which was confined to leukaemias and lymphomas. Results presented here are based on further data for these diagnostic groups together with data for the other types of childhood cancer not presented before. The analyses in this chapter and Chapter 4 are based on the International Classification of Childhood Cancer – a classification system which takes account of the particular types of cancer occurring in children and which is summarised in Table 1.1. These data relate to all forms of childhood cancer occurring in England, Scotland and Wales in the years 1969–1993. The aim in this chapter is to provide an overview of the geographical patterns of variation in the incidence of the different types of childhood cancer and to examine possible relations between these rates and a number of socio-demographic factors. In Tables 3.1–3.3 we give, for each country, Standard Region and county within Great Britain, incidence rates for the 25-year period 1969–1993 for the main forms of childhood cancer, as listed in Table 1.1. These are followed by detailed analyses of incidence in relation to selected socio-demographic factors of different forms of childhood cancer at two geographical levels: first, by county district (of which there are 459) with an average child population of 25,000; second, by census wards (of which there are 9,289 in England and Wales and 1155 in Scotland) with an average child population of about 1,100. (In Scotland a census ward is equivalent to a postcode sector; we shall refer to census wards or simply to 'wards' throughout this report.) More information about the child population of the areas used in this report is given in Table 1.2.

3.2 The socio-demographic factors used in the analyses are: 'socio-economic score' (SES), defined in Annex 3B (see p 93), paragraph 3B.12, based on the index of social deprivation (the 'Carstairs index') proposed by Carstairs and Morris (1989), 'degree of household overcrowding', and 'population density'; these are based on information available from census data and are defined in paragraphs 3B.13 and 3B.14. In addition, county districts and wards are each classified according to their 'urban/rural status', or degree of urbanisation, as explained in paragraphs 3B.15 and 3B.17. Differences in the levels of these factors might be related to variations in the incidence of childhood cancers. There is evidence that childhood leukaemia (unusually among childhood

illnesses) may be more common at higher levels of SES. The analyses of incidence rates in relation to overcrowding are of particular interest for two reasons: first, this variable is a measure of socio-economic status – and is indeed a component of, and highly correlated with, the Carstairs index used in this report; second, it may be a better measure of exposure than SES to infectious agents and hence be of relevance to theories relating such agents to either an increase or a decrease in the incidence of leukaemia and other childhood cancers. Both population density and degree of urbanisation may be related to infections and other environmental factors affecting disease incidence. As explained in paragraph 3B.17, differences in definition of the urban/rural classification between England/Wales and Scotland have made it necessary to analyse England and Wales wards separately from those for Scotland. This does, however, have the advantage of providing two sets of results for each factor, and these results can be compared to see whether they are consistent. In most of the analyses in this chapter we have used *age-standardised rates (ASRs*) – see the glossary – rather than the incidence rates for individual age groups. The ASRs are in one sense more appropriate for these analyses because they involve larger numbers of cases and because analysis by age group would create three times as many tables; on the other hand, we have found in certain diagnostic categories that some findings of interest relate to one or two specific age groups. These are referred to below.

Results

3.3 Results from these analyses are given in Tables 3.1–3.13 (pp 35–90). These tables are described in paragraphs 3.4–3.12 and the findings discussed in paragraphs 3.13–3.39. A large number of more detailed tables is available on the CCRG website (www.ccrg.ox.ac.uk/COMARE11). Lists of all tables in this report and on the website are given in Tables 3A and 3B respectively (see pp 33 and 34). Incidence rates are presented as cases per million children per year; this is in contrast to the usual presentation of corresponding rates for adults, where cancer is much more common and rates are presented as cases per 100,000 per year.

Rates for Great Britain

3.4 Table 3.1 gives the national age-specific and age-standardised rates for each of the main diagnostic categories. In Great Britain over the 25-year period there were just over 32,000 cancers in children, ie about 1300 per year, giving an overall rate of 112.9 per million per year. Of these about one-third were leukaemias, one-tenth lymphomas, and about one-quarter malignancies of the brain and central nervous system. Differences in the age distributions of the different cancers can be clearly seen in this table. The majority of leukaemias (mainly acute lymphoblastic leukaemia), retinoblastoma and other characteristic embryonal tumours of children – neuroblastoma, Wilms' tumour and hepatoblastoma (not shown separately in Table 3.1) – occur in the first few years of life, while lymphomas, bone tumours and carcinomas appear most frequently at ages 10–14 years.

Rates for countries of Great Britain, and for English Standard Regions

3.5 Table 3.2 gives the ASRs for each of the main diagnostic groups for the Registrar General's Standard Regions in England. Subtotals for England, Wales and Scotland are also given. Moreover, this table gives the result of a statistical significance test comparing regional differences (ie those for English Standard Regions, Wales and Scotland) in the crude incidence rates (not the ASRs) at ages 0–14 years. It can be seen that for some of the diagnostic groups there is considerable regional variation in the rates: these differences are statistically significant for several of the diagnostic groups and for the total. For the latter the ASRs vary between 122.5 per million (East Anglia) and 107.4 (Wales), a ratio of 1.14. For leukaemia the rates vary between 41.7 (South West) and 34.2 (Wales), a ratio of 1.22. The findings are discussed in paragraph 3.25.

Rates for counties and countries of Great Britain

3.6 Table 3.3 gives the ASRs for each of the main diagnostic groups for each of the counties in Great Britain. Totals for England, Wales, England and Wales, and Scotland, and for Great Britain are also given. In the counties of England and Wales the rates for all cancers combined vary between 132.2 per million (Buckinghamshire) and 94.1 (West Glamorgan), a ratio of 1.40. For leukaemia the rates varied between 48.3 (Buckinghamshire) and 29.1 (West Glamorgan), a ratio of 1.66. Leukaemia rates in Scotland show greater variability (from 62.8 to 33.1) because the much smaller populations, particularly of the Islands areas, result in proportionately greater random fluctuations in the numbers of cases. The findings are discussed in paragraph 3.26.

Rates for county district and wards categorised by values of socio-demographic variables

Incidence rates for categories of county districts

3.7 The results of the analyses of age-standardised rates for county districts grouped according to quintiles of socio-demographic factors are given in Table 3.4, for each of the main diagnostic groups and the subgroups listed in Table 1.1.

Incidence rates for categories of census wards

3.8 The results of the analyses of age-standardised rates for wards grouped according to quintiles of socio-demographic factors are given in Tables 3.5 (England and Wales) and 3.6 (Scotland). In these tables the last two columns show the results of the Poisson regression analyses of the variations in rates between these groups of wards (see paragraph 3B.18 and Tables 3.10 and 3.11). The penultimate column indicates the level of statistical significance of differences in the crude incidence rates (again, not the ASRs) between the groups; the final column shows the results of the statistical test for trend, ie the test of whether there is a significant increase or decrease in the incidence rates in relation to the levels of the factor represented by the columns.

Rates for two-way classifications for county districts and for census wards

3.9 In Table 3.7 county districts are categorised simultaneously as being in the top, middle or bottom third of each of a pair of the factors of interest, and ASRs for selected tumour groups tabulated for each of the nine joint categories. With these tables we can examine whether, at county district level, the effect of an individual factor persists when some other factor is allowed for or whether the second is immaterial when the first is allowed for. Similarly, in Tables 3.8 and 3.9 the ASRs for wards are tabulated by two factors simultaneously. These tables make it possible to examine the question of whether, at ward level, the effects for individual factors in Tables 3.5 and 3.6 persist when a second factor has been allowed for. It should be noted that at ward level some of the joint categories contain very small populations, and spuriously high and low rates are likely to be found.

3.10 The findings for county districts and census wards are discussed and compared in paragraph 3.27.

Poisson regression analyses for ward incidence rates

3.11 Another way of assessing the effects of two factors simultaneously is to analyse the incidence rates by means of Poisson regression analysis (see paragraph 3B.18). This makes it possible to assess the effect of single factors and of including a second factor when the effect of one factor has already been allowed for. The effects of individual factors, and of adding a second factor, on the crude incidence rates at age 0–14 years are summarised for each diagnostic group in Tables 3.10 (England and Wales) and 3.11 (Scotland). In these tables we present the results of these regression analyses in the form of relative risks (RR) for the levels of the three socio-demographic factors: socio-economic score (SES), population density, and overcrowding. As already pointed, out the factor ‘overcrowding’ is of interest both in its own right and as a component of

the Carstairs index, the SES. Subsidiary analyses were carried out using the other individual components of the index described in paragraph 3B.12. The RR estimates are calculated as incidence rate ratios, ie the estimated incidence rate for each factor level relative to the specified reference level. Estimates of the RR for the levels of each factor are also given having first adjusted for the effect of each of the other factors (except for the combination of SES and overcrowding, these factors being too closely correlated). For England and Wales, estimates that allow for the effect of differences between regions are also presented. In these tables the unadjusted RRs, ie the first set of values for each factor in each diagnostic group, are equivalent to the absolute values of the corresponding rates presented in Tables 3.5a,b,c and 3.6a,b,c. Statistical tests for heterogeneity and trend are given in the final two columns. For the unadjusted values these are the same as in Tables 3.5 and 3.6. (See paragraphs 3.8 and 3B.18 for an explanation of these analyses.)

Incidence rates and Poisson regression analyses for individual age groups

3.12 In order to allow for the possibility that, within a diagnostic group, cases diagnosed at different ages could reflect aetiologically diverse subgroups having different age distributions, further analyses have been carried out: incidence rates for age groups 0–4, 5–9 and 10–14 years have been calculated both for county district and for wards categorised by values of the socio-demographic factors; tables analogous to Tables 3.4, 3.5 and 3.6 have been created. Poisson regression analyses similar to those in Tables 3.10 and 3.11 have been calculated for various age groups. In some cases there is no obvious difference between the age groups; in others the numbers were too small for any meaningful analysis. Some of the results are reported below. Detailed results are on the CCRG website (www.ccrg.ox.ac.uk/COMARE11).

Overview of findings for each diagnostic group

Leukaemia

3.13 There is highly statistically significant variation by region, the highest rates being found in the South West and the lowest in Wales. The socio-economic status (SES) variable is strongly related to levels of leukaemia incidence at both county district and ward level, as can be seen from Tables 3.4a, 3.5a and 3.6a and the results of the Poisson regression analysis (Tables 3.10a and 3.11a). Table 3.10a also shows that the regional and SES effects are each significant (though less so) when the other is allowed for; at least part of the regional effect appears to be due to differences in SES. However, the SES effect does not seem to be simply attributable to regional effects. Incidence rates are higher in areas of higher SES, though the highest rate is in the second highest SES group at both county district and ward level. The largest subgroup in the childhood leukaemia group is acute lymphoblastic leukaemia (ALL). As explained in the note to Table 1.1, most cases recorded as ‘unspecified leukaemia’ in childhood, and all ‘lymphoid’ leukaemia, will in fact be ALL. We have therefore presented results for this, mainly ALL, subgroup which accounts for about 80% of childhood leukaemia; the results are very similar to, and stronger than, those for the all leukaemias group. The tables and analyses for separate age groups on the website (www.ccrg.ox.ac.uk/COMARE11) show further that this effect is strongest for those aged 1–4 and 5–9 years. Similar results are found for the analyses in relation to overcrowding (which is a component of the Carstairs index for SES), again suggesting that higher rates are associated with better living conditions. From Tables 3.4c, 3.5c and 3.6c it can be seen that, at both county district and ward level, incidence increases as population density decreases. Correspondingly, at county district level, Table 3.4d suggests that the age-standardised rate increases slightly in the more rural areas, though, as explained in paragraph 3B.15, the classification of county districts for this variable may be misleading. When the effects on incidence of two factors simultaneously are considered, either by examination of the two-way tables or using the regression

analyses involving two variables, it is clear that the effects of socio-economic score or overcrowding are, at least to some extent, independent of those for population density or urban/rural status.

Lymphomas and reticuloendothelial neoplasms

3.14 In this group it is necessary to consider separately the results for Hodgkin lymphoma and for non-Hodgkin lymphoma (NHL). For NHL there is some similarity in the effects of the socio-demographic variables to those found for ALL, though the effects are not very strong (Tables 3.4a,b,d and 3.5a,b). For Hodgkin lymphoma the results for the age groups 0–4 and 5–9 years show a completely different pattern. For these younger age groups both the tables for county districts and wards and the Poisson regression analyses show higher rates are associated with *greater* levels of overcrowding and *greater* degree of social deprivation (in England and Wales, though not in Scotland), in contrast to the findings for leukaemia and NHL. The results for ages 0–9 years are summarised in Table 3.13. The rationale underlying this particular analysis and a discussion of these very striking results is given in paragraph 3.33.

CNS and miscellaneous intracranial and intraspinal neoplasms (CNS)

3.15 Tables 3.4a for county districts and 3.5a for wards show that the age-standardised rates decrease with increasing degree of social deprivation for CNS tumours. Tables 3.4b and 3.5b show a relation between overcrowding and these rates – the effect being in the same direction as for the Carstairs index, ie higher rates are associated with better living conditions. From Tables 3.4c, 3.5c and 3.6c it can be seen that the incidence of CNS tumours increases as population density decreases at both county district and ward level.

Sympathetic nervous system tumours

3.16 For this group, almost entirely neuroblastoma, there are no noteworthy findings.

Retinoblastoma

3.17 Epidemiological studies of retinoblastoma usually consider separately bilateral cases, invariably heritable and behaving as an autosomal dominant condition, and unilateral cases, which are usually not heritable. The majority of the heritable cases do not have a previous family history; this suggests that most of them are probably the results of *de novo* mutations. There are significant regional differences for the unilateral type but not for the bilateral type (Table 3.10e). There is no evidence of systematic variation in relation to the socio-demographic factors considered.

Renal tumours

3.18 High incidence rates are found for renal tumours in Cornwall and Wiltshire and some other southern and western counties and in the Borders region of Scotland. There is a non-significant trend suggesting that the age-standardised rates decrease with increasing degree of social deprivation for renal tumours. The detailed tables and regression analyses show that this effect is strongest at younger ages, where most of the cases occur; the great majority of these will be Wilms' tumours.

Hepatic tumours

3.19 In children the majority of these tumours are hepatoblastomas, an embryonal tumour, and a minority are carcinomas. There are regional differences which affect both types; the effect is statistically significant for hepatoblastoma but not for hepatic carcinoma, though this may be a consequence of the smaller numbers in this latter group. There is no indication that the regional effects can be explained, even in part, by an SES effect.

Malignant bone tumours

3.20 Tables 3.4a,b and 3.5a,b suggest that the age-standardised rates decrease with increasing degree of social deprivation (as measured by either SES or overcrowding) for malignant bone tumours at both county district and ward level. More detailed examination of the tables on the website suggests that this effect is seen mainly at ages 10–14 years (though the majority of childhood bone tumours occur at these ages). The effect seems to be confined to Ewing's sarcoma; there is little indication of such an effect for osteosarcoma. (These two diagnoses account for most childhood bone tumours.) Cambridgeshire has a notably high rate of bone tumours.

Soft-tissue sarcomas

3.21 There is little evidence of variation between areas in relation to SES but some suggestion of low rates in areas of high population density.

Germ cell, trophoblastic and other gonadal neoplasms

3.22 This rather mixed group of relatively uncommon tumours taken together shows little evidence of variation in incidence in relation to the socio-demographic factors considered here.

Carcinoma and other malignant epithelial neoplasms

3.23 The incidence of carcinomas etc is higher in areas of high SES. In the regional analyses generally the most striking of the elevated rates is that for carcinomas and other malignant epithelial neoplasms in the Borders Region of Scotland. It can be seen from column 11 of Table 3.3 that the rate in the Borders is 13.5 (based on seven cases). These seven cases were all coded as melanomas and a more detailed investigation by Dr David Brewster, the Director of the Scottish Cancer Registry, has confirmed that all but one have been correctly coded. When the incorrectly coded case is removed from the analysis the rate is reduced to 11.6 which is still strikingly higher than the national rate of 3.0, and the rate of 7.2 for the Isle of Wight, the next highest county. In other counties the raised rates for this group are not solely due to melanoma. We note also that the increase in melanoma observed in the Borders is not found in more recent years or in adjacent counties. Pathological review of cases diagnosed as melanoma in childhood in the west of Scotland during 1979–2002 considered many of them to be unusual naevi rather than melanoma (Leman et al, 2005). We think that these findings might apply to some of the cases in this present report, those in the Borders and elsewhere.

Discussion: regional variations

3.24 The differences in rates in Tables 3.2 and 3.3 may reflect regional differences in aetiologically important factors, differences in ascertainment rates or purely chance variations. In paragraphs 3.25 and 3.26 we discuss some possible explanations for these findings.

Variation in rates between English Standard Regions, Scotland and Wales

3.25 The differences in rates observed in Table 3.2 will be partly due to chance; however, the results of the tests for statistical significance reported at the foot of this table indicate that it is extremely unlikely that this is the complete explanation. The differences in rates may also be due to differences in ascertainment of cases; the fact that the pattern of high and low rates is different for different diagnostic groups makes it unlikely that this is the whole explanation and, moreover, the Standard Regions for which results are presented are not coterminous with the Registry Regions that are responsible for cancer registration.

Variations in rates between counties

3.26 Similarly, the rates for counties in Table 3.3 suggest that the pattern of incidence of childhood cancer is not uniform across the country. For leukaemia the range of variation is similar to that reported by Stiller et al (1991) based

upon data for 1969–1983. In general, as for differences between regions, the patterns differ between diagnostic groups, ie counties with higher than average rates for some cancers have lower than average rates for others. It is not clear how much of this is simply due to random variation, ie whether the variation observed between counties is simply a consequence of chance or, if not, what other factors might be influencing the observed patterns, or whether there are differences in the recognition and notification of cases in different parts of the country. Some of these high rates may give clues to aetiological factors.

Comparisons between analyses at county district and census ward levels

3.27 One reason for analysing the results at two very different geographical levels was that it seemed likely that any relationships between the socio-demographic factors and incidence rates would be more marked at ward level, since these smaller areas would be more homogeneous, eg that the known effect of socio-economic status on leukaemia rates at county district level would show up more strongly in the analysis at ward level. Little evidence for this was found, and it was then hypothesised that the explanation could be that wards would be likely to change in nature over a 25-year period and that a more appropriate analysis would be to examine the rates for a 10-year period surrounding the 1981 census, since values for socio-economic score etc calculated from the 1981 census should reflect the situation in the ward more closely for 1976–1985 than they would for the longer period 1969–1993: any relation between the incidence rate and these variables should therefore be stronger for this 10-year period. We have tabulated results for wards using only data for this period; these tables are included on the website but not in this report. In Table 3.12, as an example, we give the rates at ages 0–4 years for leukaemia and CNS tumours respectively for county districts and England and Wales wards over the 25-year period, and England and Wales wards over the 10-year period, subdivided in each case by the Carstairs index of socio-economic status. For both diagnostic categories incidence tends to be higher for the least deprived category; for leukaemia, but not CNS, there is some evidence of a greater difference between the socio-economic groups for the 1976–1985 wards. Although this difference is not very marked, it is somewhat greater if one compares the rate for 1976–1985 with those for the remainder of the 25-year period, ie 1969–1975 + 1986–1993.

Discussion: aetiological factors

3.28 We discuss here the findings of the above analyses in relation to the epidemiology of childhood cancer more generally and, in particular, in relation to theories concerning the possible importance of infections in the aetiology of leukaemia and some other cancers. A summary of aspects of the aetiology of childhood cancer, particularly in relation to the part played by infectious agents, is included in Chapter 2. The most notable finding reported below is the higher incidence rate found for several diagnostic groups in areas of higher SES. This association has been previously reported for childhood leukaemia but, as far as we are aware, there has been no previous analysis on a comparable scale for other childhood cancers. The analyses for the effect of overcrowding, a component of the Carstairs SES index, gave similar results to those for SES. We also carried out a more limited series of analyses using the other components of this index (see paragraphs 3.11 and 3B.12) with generally similar results. It is of course theoretically possible that the association between higher incidence and high SES is due to better diagnosis in more affluent areas.

Analyses of socio-demographic factors in relation to childhood leukaemia

3.29 The results presented for leukaemia in relation to socio-economic status and, to a lesser extent, those for the urban/rural classification and population density are in line with previous research findings. It should be noted that although some statistically highly significant results are obtained in the regression analyses, it is clear from the detailed analysis of deviance (not shown here) that the factors analysed account for only a small proportion of the

variation at ward level. Thus the variations in rates must be due to other factors, or to differences in ascertainment or simply to random variation.

3.30 There is at present great interest in, and considerable evidence for, theories relating childhood leukaemia to exposures to infection. These ideas, and particularly the theories of Kinlen and Greaves, are discussed in Chapter 2. Kinlen has shown in a series of studies that childhood leukaemia rates increase as a consequence of 'population mixing' (see the glossary), typically when there is an influx of newcomers to rural areas, and has suggested that this increase supports the hypothesis that there is an infectious basis for at least some cases of childhood leukaemia. (Though there is no suggestion that leukaemia can be passed from one child to another.) A paper to be submitted for publication (Stiller, personal communication), the abstract of which is reproduced here as Annex 3A (p 91), gives further support to Kinlen's theory. Greaves has postulated that, in the case of acute lymphoblastic leukaemia, early protection from, and subsequent exposure to, infectious agents generally may lead to cell proliferation and expansion of a leukaemic clone. In contrast, Kinlen suggests that there is a specific agent or agents involved. The relation of leukaemia incidence rates to measures of socio-economic status, of overcrowding, and of urban/rural differences, appears to be consistent with these hypotheses and thus to lend support to theories concerning a possible infectious component in the aetiology of childhood leukaemia. It can be seen from Tables 3.4b, 3.5b and 3.6b that higher levels of overcrowding (which could reasonably be assumed to lead to higher levels of infection) are associated with *lower* levels of leukaemia. This effect is stronger for wards than for county districts, stronger when the ten years most appropriate to these census-based variables are considered, and again stronger for lymphoid and unspecified leukaemia, essentially ALL, than for all leukaemias together. This association of higher levels of overcrowding with lower levels of leukaemia might seem to argue against a population-mixing hypothesis – but it is not in fact inconsistent, since that hypothesis is concerned with exposure to *new* infections and thus possibly with an increase in overcrowding – not with overcrowding *per se*. It is also consistent with the suggestion of Greaves that the risk of leukaemia is increased by delayed exposure to infection. The regression analyses give similar results for the overcrowding and socio-economic status variables in relation to leukaemia. It is well known that Epstein-Barr virus is involved in the causation of some cases of Hodgkin lymphoma. In a recent paper, Lehtinen et al (2003) found an association between this virus and ALL: EBV reactivation was more likely in pregnancies where the child developed ALL than in pregnancies of controls.

Analyses of socio-demographic factors in relation to childhood cancers other than leukaemia

3.31 The results relating to socio-demographic factors for the remaining cancers are new and perhaps rather surprising in that the observed patterns are similar to those for leukaemia. This raises questions as to whether the hypotheses concerning infectious agents invoked to explain the leukaemia findings might also apply to some other childhood cancers. Nearly all of the earlier studies have been concerned with childhood leukaemia rather than other childhood cancers; these new findings raise questions concerning possible mechanisms through which infection might be involved in the aetiology of these cancers. In paragraphs 3.32–3.39 we discuss those diagnostic groups for which positive findings in relation to socio-demographic factors are reported in paragraphs 3.13–3.23.

Non-Hodgkin lymphoma

3.32 Aetiological studies of childhood leukaemia have frequently grouped this condition with leukaemia on the assumption that the two groups (or at least NHL and ALL) are aetiologically similar. The finding reported in paragraph 3.14

that associations between socio-demographic factors and NHL are similar to those for ALL, though weaker, is in line with this assumed similarity and suggests that the underlying causes may be similar in at least some respects.

Hodgkin lymphoma

3.33 For Hodgkin lymphoma at ages 0–9 years (see Table 3.13) the trend in relation to socio-economic-score/overcrowding is reversed. Previous epidemiological findings (see, for example, Little 1999) provide evidence for there being a different aetiological relationship to infection for this disease. Hodgkin lymphoma in younger children tends to be of the mixed cellularity subtype which is associated with Epstein-Barr virus (cf paragraph 2.19). As part of the general series of analyses of socio-demographic factors carried out for individual age groups (see www.ccrg.ox.ac.uk/COMARE11) we looked in detail at the effects of SES and overcrowding for separate age groups. The specificity and strength of the association between Hodgkin lymphoma at ages 0–9 years and these socio-demographic effects, and the fact that this hypothesis had been suggested by earlier studies, very strongly suggests that this association is real.

CNS tumours

3.34 CNS tumours are the most common forms of childhood cancer after leukaemia. Perhaps the most striking finding of this series of analyses is the strong relation, as for leukaemia, between the incidence of this type of tumour and higher socio-economic status. This obviously raises the possibility of an infectious element in the aetiology of these tumours. There appear also to be effects of both regions and population density on incidence, the rates being highest in East Anglia and in areas of low population density. It would be unwise to suggest specific aetiological mechanisms in the absence of further information.

Retinoblastoma

3.35 The significant regional variation in the incidence of retinoblastoma appears to be due to variations in the unilateral type of this disease rather than in the bilateral type. The bilateral type is invariably associated with a germ-cell mutation in the RB1 gene, whereas most unilateral cases do not have this germ-cell mutation. Thus geographical variations in the frequency of bilateral cases will reflect differences in mutation frequency, whereas differences in frequency of unilateral cases, as found in the present data, may reflect other types of environmental influences. There are known to be international variations in the incidence of this cancer. This could be due to differences in exposure to infectious agents; there is evidence (Orjuela et al, 2000) that viruses may be implicated in the causation of retinoblastoma. It has also been suggested (Hooper, 1999) that the international variations may be associated with variations in latitude (and hence perhaps exposure to sunlight, though this explanation has been questioned by Jemal et al, 2000).

Renal tumours

3.36 The great majority of renal tumours in children are the embryonal tumour, Wilms' tumour. There is a slight suggestion of higher incidence associated with higher SES.

Bone tumours

3.37 The main finding for bone tumours is the decrease in incidence with increasing degree of social deprivation. This effect is not found for osteosarcoma but only for Ewing's sarcoma. It is well known that the incidence of this tumour is low in black populations both in the USA and in Africa, and it would be of considerable interest to explore any possible connection between that association and the results presented here.

Soft-tissue sarcomas

3.38 There is some suggestion of low rates in areas of high population density.

Carcinomas

3.39 The incidence of carcinomas etc is higher in areas of high SES.

Comparisons with previous analysis

3.40 Until now the main reference for studies of this type has been a series of analyses of an earlier dataset (Draper, 1991), though this was concerned only with leukaemia and non-Hodgkin lymphoma. The findings for leukaemia in relation to socio-economic score and urban/rural status in the present study are in agreement with those published there. This gives some support to the present findings, though there is considerable overlap between the two sets of analyses.

Relevance to interpretation of findings around nuclear installations

3.41 These analyses show the extent to which variations in rates can reasonably be attributed to geographical variation or to certain explanatory variables. The differences between the various groupings analysed here, mainly divisions by quintiles of the levels of the factors analysed, tend to give incidence rates varying by at most 25%. It is of course possible that if we consider more extreme values of the factors, and perhaps particular combinations of them, we shall find greater variation in risk, though it seems unlikely that a rate ten times the average as found in Seascale will be common. Current studies of clustering, eg those reported in Chapter 4, will provide information on the extent to which clustering is part of the natural history of childhood leukaemia and other cancers of childhood.

Summary

- *Interpretation of statistically significant findings* As in any large series of analyses, it is essential to interpret very cautiously the statistically significant findings presented here: in such analyses multiple testing may be expected to give some statistically significant findings simply as a result of chance. (In addition, the findings relating to extra-Poisson variation in Chapter 4 may invalidate the actual significance levels.) We have drawn attention to results that are particularly striking, that are internally consistent, and that can be related to other studies of childhood cancer. There are some other results that are new, and for some of these it seems reasonable to speculate on possible aetiological mechanisms while emphasising the need for caution and for confirmation from other studies.

- The most important finding from this chapter is that the previously accepted relationship between childhood leukaemia and higher socio-economic status (which may be a marker of reduced early exposure to infection) appears to extend also to some other forms of childhood cancer. *(Paragraphs 3.14, 3.15, 3.18, 3.20 and 3.23)*

- In particular, for CNS tumours this relation appears to hold; but it seems also that there is also a relation with population density, rate increasing with lower density. *(Paragraphs 3.15 and 3.34)*

- In contrast to these findings, Hodgkin lymphoma at ages 0–9 years is found to be more common in areas of low socio-economic status and is very strongly associated with overcrowding; this is consistent with previous results concerning the importance of early exposure to Epstein-Barr virus in the causation of this disease in this age group. *(Paragraph 3.33)*

- Some findings, eg that relating to melanoma in the Borders Region, need evaluating in relation to other aetiological studies of cancers, eg the geographical variations in both child and adult melanoma in Britain. *(Paragraph 3.23)*

- It should be emphasised that, although some of the findings are highly statistically significant the factors measured here account for only a small part of the variation in the incidence of childhood cancers. This may be because they are, in effect, proxies for underlying factors that have a closer relation to childhood cancer, ie there may be related factors that that have more important effects than those we have been able to measure. The main causes of these diseases appear likely to be factors unrelated, or only slightly related, to those considered here.

- *Conclusions from Annex 3A on population mixing* (as explained in paragraph 3.30 and Annex 3A, these are unpublished data and results) For ALL at ages 1–4 years in England and Wales, there was a tendency for higher incidence to occur in wards with a higher diversity of previous ward of residence of recent incomers and, independently, in rural areas. The effect of the Carstairs index of deprivation was much weaker when population mixing was allowed for, and *vice versa*. No evidence of association with population mixing or deprivation was found for ALL diagnosed at ages 0, 5–9 or 10–14 years. The apparent specificity of the association to the young childhood age group is consistent with the hypothesis put forward by Greaves (see paragraph 2A.11). The association with incomers' diversity, particularly in rural areas, is consistent with the hypothesis put forward by Kinlen (see paragraph 2A.10).

Table 3A Summary of tables included in Chapter 3

Tables of incidence rates					
Table	**Diagnosis***	**Age group**	**Period**	**Area**	**Categorisation of area**
3.1	Standard	0–4, 5–9, 10–14, 0–14	1969–1993	Great Britain	
3.2	Standard	0–14	1969–1993	England, Wales and Scotland English regions	
3.3	Standard	0–14	1969–1993	Counties and countries	
3.4a–d	Standard and subgroups	0–14	1969–1993	Great Britain: county districts	Socio-economic score, overcrowding, population density, urban/rural
3.5a–d	Standard and subgroups	0–14	1969–1993	England and Wales wards	Socio-economic score, overcrowding, population density, urban/rural
3.6a–d	Standard and subgroups	0–14	1969–1993	Scottish wards	Socio-economic score, overcrowding, population density, urban/rural
3.7a–f	Leukaemia CNS All cancer minus leukaemia Lymphoid and unspecified leukaemia NHL All cancer	0–14	1969–1993	Great Britain: county districts	By pairs of factors: Socio-economic score, overcrowding, population density, urban/rural
3.8a–f	Leukaemia CNS All cancer minus leukaemia Lymphoid and unspecified leukaemia NHL All cancer	0–14	1969–1993	England and Wales wards	By pairs of factors: Socio-economic score, overcrowding, population density, urban/rural
3.9a–f	Leukaemia CNS All cancer minus leukaemia Lymphoid and unspecified leukaemia NHL All cancer	0–14	1969–1993	Scottish wards	By pairs of factors: Socio-economic score, overcrowding, population density, urban/rural

* Standard diagnostic groups are specified in Table 1.1 and may sometimes include summary groups, ie total (for all cancer) and total leukaemia. Subgroups are those identified as being of particular interest. 'Main' groups are leukaemia, CNS, total leukaemia; 'ALL/NHL' represents the groups 'lymphoid leukaemia and unspecified leukaemia' and 'non-Hodgkin lymphoma (NHL only)'.

Table 3A Continued

Results of regression analyses					
Table	**Diagnosis***	**Age group**	**Period**	**Area**	**Categorisation of area**
3.10a–n	Standard and subgroups	0–14	1969–1993	England and Wales wards	Standard region, socio-economic score, overcrowding, population density
3.11a–n	Standard and subgroups	0–14	1969–1993	Scottish wards	Socio-economic score, overcrowding, population density
Supplementary tables					
Table	**Diagnosis***	**Age group**	**Period**	**Area**	**Categorisation of area**
3.12a,b	Leukaemia CNS	0–4	1969–1993 1976–1985	Great Britain: county districts England and Wales wards	Socio-economic score
3.13	Hodgkin lymphoma	0–9	1969–1993 1976–1985	GB county districts England and Wales wards Scottish wards	Socio-economic score, overcrowding, population density, urban/rural

* Standard diagnostic groups are specified in Table 1.1 and may sometimes include summary groups, ie total (for all cancer) and total leukaemia. Subgroups are those identified as being of particular interest. 'Main' groups are leukaemia, CNS, total leukaemia; 'ALL/NHL' represents the groups 'lymphoid leukaemia and unspecified leukaemia' and 'non-Hodgkin lymphoma (NHL only)'.

Table 3B Summary of tables to be available on the CCRG website: www.ccrg.ox.ac.uk/COMARE11

More detailed tables than those provided in Chapter 3, and listed in Table 3A, will be made available as follows
Tables as 3.4–3.6 as described in Table 3A but giving five-year age-specific incidence rates as well as the 0–14 years age-standardised incidence rate.
Tables as 3.5 and 3.6 for England/Wales wards and Scottish wards, respectively, but for the shorter time period 1976–1985. Five-year age-specific incidence rates and 0–14 years age-standardised incidence rate.
Table as 3.8 for England/Wales wards but for the shorter time period 1976–1985.
Tables as 3.10 and 3.11 (regression analysis) but by five-year age groups.

Table 3.1 Age-specific and age-standardised rate (per million children) for Great Britain 1969–1993

Diagnostic group	Age (years) males and females								
	0–4		5–9		10–14		0–14		
	No	Rate	No	Rate	No	Rate	No	Rate	ASR +
1 Leukaemias	5645	60.8	2970	30.8	2122	21.4	10737	37.2	37.7
2 Lymphomas and reticuloendothelial neoplasms	587	6.3	1094	11.3	1625	16.4	3306	11.5	11.4
3 CNS and miscellaneous intra-cranial and intra-spinal neoplasms	2625	28.3	2652	27.5	2197	22.2	7474	25.9	26.0
4 Sympathetic nervous system tumours	1671	18.0	317	3.3	123	1.2	2111	7.3	7.5
5 Retinoblastoma	901	9.7	41	0.4	3	0.0	945	3.3	3.4
6 Renal tumours	1449	15.6	359	3.7	82	0.8	1890	6.6	6.7
7 Hepatic tumours	183	2.0	34	0.4	41	0.4	258	0.9	0.9
8 Malignant bone tumours	79	0.9	383	4.0	1045	10.5	1507	5.2	5.1
9 Soft-tissue sarcomas	927	10.0	573	5.9	601	6.1	2101	7.3	7.3
10 Germ cell, trophoblastic and other gonadal neoplasms	473	5.1	140	1.5	370	3.7	983	3.4	3.4
11 Carcinoma and other malignant epithelial neoplasms	107	1.2	195	2.0	578	5.8	880	3.1	3.0
12 Other and unspecified malignant neoplasms	51	0.5	34	0.4	46	0.5	131	0.5	0.5
All cancer	14698	158.4	8792	91.2	8833	89.1	32323	112.1	112.9

+ ASR = age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.2 Age-standardised rates [+] (per million children) by diagnostic group by country and English standard regions for 1969–1993

	Diagnostic group #													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**	**Cases**
English Regions														
North	36.9	11.4	26.4	8.0	4.5	6.3	0.7	5.0	7.8	3.5	3.2	0.4	114.1	1872
Yorkshire and Humberside	37.1	11.9	26.0	7.6	2.9	6.4	0.9	5.0	7.1	3.7	2.8	0.2	111.7	2909
East Midlands	38.5	11.4	26.0	7.4	3.4	7.4	0.9	5.6	7.9	3.4	2.3	0.6	114.9	2341
East Anglia	38.1	12.6	28.5	8.7	4.2	7.0	0.2	6.5	8.2	4.3	4.0	0.3	122.5	1189
South East	38.5	11.7	24.9	7.7	2.9	6.8	1.0	5.4	7.4	3.0	2.8	0.4	112.6	9758
South West	41.7	10.6	27.4	6.8	3.4	8.0	1.0	5.3	7.8	4.0	3.9	0.8	120.6	2587
West Midlands	38.0	11.4	27.0	6.7	4.0	5.8	1.0	4.7	7.4	3.4	2.9	0.5	112.9	3181
North West	34.8	10.1	27.8	6.7	3.1	6.5	1.2	4.7	6.2	3.9	3.2	0.2	108.4	3792
England	37.9	11.3	26.2	7.4	3.3	6.7	1.0	5.2	7.3	3.4	3.0	0.4	113.3	27629
Wales	34.2	11.1	22.3	8.3	3.7	6.7	0.2	5.0	8.1	3.5	3.4	1.0	107.4	1573
Scotland	37.2	11.5	25.9	8.0	4.0	6.6	0.8	4.6	6.8	3.3	2.8	0.5	112.0	3121
p for heterogeneity ++	***	-	**	-	*	-	**	-	-	-	-	**	***	

 # Key to diagnostic group

1 Leukaemias
2 Lymphomas and reticuloendothelial neoplasms
3 Central nervous system and miscellaneous intra-cranial and intra-spinal neoplasms
4 Sympathetic nervous system tumours
5 Retinoblastoma
6 Renal tumours
7 Hepatic tumours
8 Malignant bone tumours
9 Soft-tissue sarcomas
10 Germ cell, trophoblastic and other gonadal neoplasms
11 Carcinoma and other malignant epithelial neoplasms
12 Other and unspecified malignant neoplasms

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

++ Heterogeneity of crude incidence rates between English regions, Wales and Scotland

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.3 Age-standardised rates [+] (per million children) by diagnostic group by county and country for 1969–1993

	Diagnostic group [#]													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**	**Cases**
Counties														
Inner London	37.8	12.4	22.0	7.9	2.6	6.4	1.2	4.5	7.1	2.4	2.5	0.4	107.2	1356
Outer London	38.1	10.8	22.7	7.2	2.4	6.6	0.9	6.2	6.5	2.5	2.6	0.3	106.7	2289
Greater Manchester	36.4	9.7	26.6	6.8	3.8	5.8	1.1	5.1	5.4	4.3	3.4	0.3	108.6	1559
Merseyside	33.9	10.2	30.8	6.0	1.9	6.8	1.1	5.1	6.4	2.6	3.1	0.1	108.0	908
South Yorkshire	40.0	10.0	27.2	5.5	2.4	6.1	1.0	3.6	7.3	4.1	3.2	0.3	110.8	763
Tyne and Wear	39.4	11.6	24.7	8.7	5.2	6.2	0.7	4.4	8.2	3.7	3.4	0.7	116.8	703
West Midlands	37.0	11.4	26.2	7.6	4.5	5.7	0.8	4.6	6.5	3.8	3.1	0.6	111.6	1656
West Yorkshire	34.9	14.5	23.1	8.6	2.6	6.5	0.8	5.2	7.6	3.6	3.2	0.3	110.8	1246
Avon	41.1	12.2	28.0	5.9	3.8	7.5	0.6	5.4	7.2	5.0	4.0	0.4	121.1	563
Bedfordshire	35.8	11.7	24.3	6.5	3.4	3.7	0.3	5.5	5.5	2.1	3.1	0.3	102.2	299
Berkshire	42.7	14.6	27.7	7.6	2.1	8.2	2.4	4.4	7.6	3.7	3.6	1.0	125.7	480
Buckinghamshire	48.3	12.4	28.4	6.4	3.8	9.5	0.0	4.9	9.1	3.7	4.0	1.5	132.2	422
Cambridgeshire	36.0	14.8	29.8	5.7	1.6	7.7	0.3	8.8	8.6	5.4	4.1	0.3	123.0	388
Cheshire	34.6	10.4	27.2	4.7	2.1	6.5	1.4	3.8	7.2	4.2	1.9	0.2	104.3	529
Cleveland	36.7	12.7	25.8	7.1	3.1	6.2	0.3	5.8	7.2	4.0	3.5	0.3	112.6	375
Cornwall	43.3	14.6	29.2	8.5	2.0	11.0	0.5	6.1	7.4	3.8	4.8	0.5	131.7	271
Cumbria	39.7	12.1	25.1	8.6	3.9	5.9	1.7	6.3	5.4	5.4	2.4	0.0	116.6	281
Derbyshire	37.9	11.9	26.1	6.7	3.9	7.2	1.1	5.5	8.0	2.5	2.7	1.1	114.6	541
Devon	39.4	9.4	28.8	7.3	2.0	7.7	0.9	6.3	7.6	3.8	4.5	0.4	118.2	534
Dorset	41.4	8.5	27.0	10.9	4.3	5.9	1.9	6.2	6.5	5.1	3.2	2.7	123.7	326
Durham	33.5	10.3	29.3	7.5	4.0	7.8	0.3	4.0	7.0	1.9	4.2	0.3	110.2	347
East Sussex	31.3	12.8	24.4	10.5	1.5	8.7	1.4	6.5	9.2	2.8	2.0	0.0	111.1	314
Essex	36.9	10.5	24.8	8.0	1.7	5.9	0.3	5.3	8.0	3.1	2.0	0.3	106.6	829
Gloucestershire	42.5	10.2	22.5	5.6	2.8	5.1	1.6	4.5	10.1	0.4	1.8	0.0	107.1	278
Hampshire	36.6	14.1	29.0	8.8	4.2	7.7	1.0	5.4	6.4	5.2	4.4	0.8	123.5	969
Hereford and Worcester	36.7	12.4	27.6	6.2	7.4	6.8	1.3	5.0	10.3	2.7	2.7	0.3	119.4	395
Hertfordshire	34.9	9.7	23.2	7.9	1.9	7.9	1.2	4.7	8.5	1.9	1.7	0.0	103.4	528
Humberside	34.8	9.3	30.8	9.5	4.7	6.0	0.7	5.6	7.3	3.4	2.3	0.0	114.3	531

Table 3.3 Continued

	Diagnostic group #													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**	**Cases**
Isle of Wight	38.2	13.3	26.4	3.8	0.0	4.1	4.1	3.6	8.0	2.0	7.2	2.0	112.7	59
Kent	41.4	11.7	24.8	6.8	4.8	6.7	0.9	5.8	8.8	3.6	1.9	0.1	117.4	906
Lancashire	33.0	10.3	27.2	8.9	3.7	7.6	1.1	4.1	6.7	4.6	3.7	0.3	111.1	796
Leicestershire	39.9	11.9	24.8	7.4	3.9	6.8	1.1	6.6	6.9	2.8	0.9	0.2	113.3	524
Lincolnshire	40.1	11.2	26.9	9.2	1.5	5.2	1.1	4.8	6.0	2.9	3.5	0.7	113.1	316
Norfolk	38.8	9.2	27.6	8.8	3.9	5.8	0.0	4.5	8.8	3.8	4.0	0.3	115.5	392
Northamptonshire	44.5	11.4	24.5	7.4	4.1	8.9	0.7	7.0	9.5	4.4	3.0	0.0	125.4	372
Northumberland	30.2	9.1	30.5	7.5	6.3	4.8	0.7	5.7	12.7	2.0	1.3	0.0	110.8	166
North Yorkshire	42.1	10.7	26.4	6.0	2.6	7.2	1.2	6.4	5.1	3.4	1.7	0.0	112.9	369
Nottinghamshire	33.6	10.7	27.2	7.1	3.1	8.4	0.7	4.4	8.8	4.2	2.4	0.9	111.6	588
Oxfordshire	37.7	10.0	31.2	10.7	3.9	8.2	0.7	2.4	6.7	2.8	3.8	0.4	118.3	337
Shropshire	41.3	15.0	28.4	6.6	3.1	5.5	1.5	5.3	8.8	1.9	2.9	1.0	121.3	246
Somerset	39.8	10.9	25.9	3.8	5.9	8.7	0.9	2.3	9.8	4.2	4.5	1.0	117.4	251
Staffordshire	39.3	9.4	28.2	6.3	0.9	5.6	1.3	4.8	6.8	4.2	2.2	0.2	109.2	597
Suffolk	39.4	14.2	28.2	11.5	7.1	7.7	0.3	6.3	7.3	3.8	3.8	0.3	129.9	409
Surrey	42.0	12.1	27.8	6.1	4.9	6.0	1.6	6.5	7.9	2.4	2.9	0.4	120.6	598
Warwickshire	40.2	11.7	28.1	3.6	4.1	5.7	0.8	4.2	9.2	2.0	3.8	0.8	114.0	287
West Sussex	41.4	10.9	27.4	10.2	1.7	6.7	1.0	5.3	10.2	3.5	2.8	0.6	121.8	372
Wiltshire	45.9	9.0	28.6	6.0	3.9	11.0	0.7	5.1	7.0	4.6	4.5	1.1	127.3	364
Total England	37.9	11.3	26.2	7.4	3.3	6.7	1.0	5.2	7.3	3.4	3.0	0.4	113.3	27629
Clwyd	35.0	12.1	23.5	10.1	1.5	4.0	0.0	3.8	8.9	5.4	5.7	0.0	109.9	224
Dyfed	34.3	11.4	21.8	6.9	3.9	10.7	0.0	4.1	8.2	4.3	4.1	1.2	110.9	181
Gwent	38.6	10.8	25.6	6.0	3.9	9.0	0.0	7.6	6.3	2.1	3.2	0.8	114.0	271
Gwynedd	29.4	10.4	28.5	8.9	2.7	7.1	0.0	2.5	6.9	1.7	4.3	0.0	102.5	118
Mid Glamorgan	34.5	14.6	19.6	8.9	3.4	6.1	0.0	5.6	7.4	4.0	2.0	2.3	108.6	322
Powys	42.5	7.0	20.6	12.0	6.0	8.0	0.0	0.0	9.7	3.7	5.6	1.8	116.9	62
South Glamorgan	32.7	9.5	23.4	6.4	6.9	5.8	1.0	5.1	8.6	2.9	2.3	0.5	105.1	219
West Glamorgan	29.1	7.8	16.9	9.9	2.8	4.4	0.5	5.6	10.2	3.2	2.6	1.1	94.1	176

Table 3.3 Continued

	Diagnostic group #													
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**Total**	**Cases**
Total Wales	34.2	11.1	22.3	8.3	3.7	6.7	0.2	5.0	8.1	3.5	3.4	1.0	107.4	1573
England and Wales	37.7	11.3	26.0	7.5	3.3	6.7	0.9	5.2	7.4	3.4	3.0	0.5	113.0	29202
Borders	35.7	6.0	25.9	2.0	2.2	14.0	2.2	2.0	1.9	0.0	13.5	0.0	105.3	52
Central	41.5	11.6	26.1	8.5	6.5	1.4	1.3	4.4	5.3	4.2	1.9	0.6	113.3	167
Dumfries and Galloway	55.3	8.5	36.8	2.8	1.4	4.3	1.4	8.5	11.7	0.0	3.6	1.2	135.6	104
Fife	41.2	15.3	33.3	10.1	4.0	8.4	1.1	7.8	6.5	3.7	1.0	0.0	132.4	245
Grampian	41.4	12.5	25.5	7.7	3.3	4.9	0.4	4.6	6.8	2.4	3.5	0.8	113.6	285
Highland	33.1	12.0	25.4	8.6	1.9	5.7	2.0	2.6	2.7	2.8	1.8	0.0	98.5	105
Lothian	33.5	11.3	30.0	9.8	4.1	7.3	1.6	4.7	8.2	4.9	2.1	0.5	118.1	446
Strathclyde	35.2	10.6	23.4	8.3	4.5	7.2	0.6	4.0	6.9	3.2	2.8	0.4	107.2	1450
Tayside	39.1	16.1	23.3	4.2	2.1	5.7	0.0	6.7	7.8	2.3	3.4	0.5	111.1	224
Orkney Islands	51.3	0.0	48.4	0.0	0.0	0.0	0.0	0.0	9.6	9.6	0.0	0.0	118.9	12
Shetland Islands	33.1	8.2	24.6	8.3	8.3	0.0	0.0	0.0	0.0	8.3	0.0	0.0	90.8	11
Western Islands	62.8	12.4	26.0	5.4	0.0	13.0	0.0	0.0	0.0	0.0	5.4	0.0	125.0	20
Total Scotland	37.2	11.5	25.9	8.0	4.0	6.6	0.8	4.6	6.8	3.3	2.8	0.5	112.0	3121
Total Great Britain	37.7	11.4	26.0	7.5	3.4	6.7	0.9	5.1	7.3	3.4	3.0	0.5	112.9	32323

 # Key to diagnostic group

1 Leukaemias
2 Lymphomas and reticuloendothelial neoplasms
3 Central nervous system and miscellaneous intra-cranial and intra-spinal neoplasms
4 Sympathetic nervous system tumours
5 Retinoblastoma
6 Renal tumours
7 Hepatic tumours
8 Malignant bone tumours
9 Soft-tissue sarcomas
10 Germ cell, trophoblastic and other gonadal neoplasms
11 Carcinoma and other malignant epithelial neoplasms
12 Other and unspecified malignant neoplasms

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.4a Age-standardised rates [+] (per million) for 1969–1993 for England, Wales and Scotland county districts subdivided into groups using quintiles of the Carstairs index of socio-economic status

Diagnostic group	Group									
	1		2		3		4		5	
	Least deprived								Most deprived	
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR
1 Leukaemias	1790	39.6	1784	40.9	1658	36.5	2203	36.7	3302	36.4
Lymphoid and unspecified leukaemia	1420	31.5	1439	33.0	1375	30.3	1778	29.7	2675	29.5
2 Lyphomas and reticuloendothelial neoplasms	567	12.2	488	10.9	503	10.9	674	11.0	1074	11.6
Hodgkin lymphoma	217	4.6	184	4.1	201	4.3	299	4.8	463	5.0
Non-Hodgkin lymphoma	304	6.6	259	5.8	260	5.6	324	5.3	531	5.8
3 CNS and misc intra-cranial and intra-spinal neoplasms	1223	26.7	1165	26.4	1196	26.1	1568	25.9	2322	25.4
Astrocytoma	462	10.1	432	9.8	454	9.9	575	9.5	903	9.9
Primitive neuroectodermal tumours (PNET)	241	5.3	256	5.8	235	5.2	323	5.3	494	5.4
4 Sympathetic nervous system tumours	348	7.8	301	7.0	354	7.9	431	7.3	677	7.5
5 Retinoblastoma	137	3.1	132	3.1	161	3.6	191	3.2	324	3.6
Retinoblastoma - unilateral	76	1.7	83	1.9	113	2.5	113	1.9	198	2.2
Retinoblastoma - bilateral	60	1.4	45	1.1	46	1.0	73	1.2	116	1.3
6 Renal tumours	342	7.7	287	6.7	298	6.7	398	6.7	565	6.3
7 Hepatic tumours	43	1.0	41	0.9	34	0.8	50	0.8	90	1.0
8 Malignant bone tumours	263	5.6	251	5.5	259	5.5	296	4.8	438	4.7
Osteosarcoma	137	2.9	127	2.8	140	3.0	164	2.6	245	2.6
Ewing's sarcoma	107	2.3	108	2.4	106	2.3	114	1.8	161	1.7
9 Soft-tissue sarcomas	340	7.5	322	7.3	373	8.2	480	8.0	586	6.4
10 Germ cell, trophoblastic and other gonadal neoplasms	148	3.2	159	3.6	159	3.5	219	3.6	298	3.3
11 Carcinoma and other malignant epithelial neoplasms	145	3.1	129	2.9	142	3.0	194	3.1	270	2.9
12 Other and unspecified malignant neoplasms	23	0.5	18	0.4	18	0.4	24	0.4	48	0.5
All cancer	5369	117.9	5077	115.7	5155	113.1	6728	111.5	9994	109.7
All cancer minus leukaemia	3579	78.3	3293	74.9	3497	76.5	4525	74.8	6692	73.4

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.4b Age-standardised rates [+] (per million) for 1969–1993 for England, Wales and Scotland county districts subdivided into groups using quintiles of degree of overcrowding

Diagnostic group	Group									
	1		2		3		4		5	
	Least overcrowded								Most overcrowded	
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR
1 Leukaemias	1461	38.7	1680	39.2	1888	37.5	2840	37.7	2868	36.5
Lymphoid and unspecified leukaemia	1162	30.9	1371	32.0	1538	30.6	2306	30.7	2310	29.4
2 Lyphomas and reticuloendothelial neoplasms	446	11.4	492	11.2	561	10.9	860	11.2	947	11.9
Hodgkin lymphoma	164	4.1	183	4.1	221	4.3	399	5.2	397	4.9
Non-Hodgkin lymphoma	247	6.4	264	6.0	301	5.9	398	5.2	468	5.9
3 CNS and misc intra-cranial and intra-spinal neoplasms	1020	26.6	1182	27.3	1350	26.5	1927	25.4	1995	25.2
Astrocytoma	378	9.8	437	10.1	533	10.5	710	9.3	768	9.7
Primitive neuroectodermal tumours (PNET)	203	5.3	238	5.5	249	4.9	427	5.6	432	5.5
4 Sympathetic nervous system tumours	293	7.9	336	8.0	359	7.2	529	7.1	594	7.6
5 Retinoblastoma	120	3.3	141	3.4	167	3.4	246	3.3	271	3.5
Retinoblastoma - unilateral	73	2.0	83	2.0	110	2.2	156	2.1	161	2.1
Retinoblastoma - bilateral	46	1.3	56	1.3	53	1.1	81	1.1	104	1.3
6 Renal tumours	257	6.9	310	7.4	360	7.2	480	6.4	483	6.2
7 Hepatic tumours	41	1.1	35	0.8	40	0.8	61	0.8	81	1.0
8 Malignant bone tumours	225	5.6	224	5.0	287	5.5	378	4.9	393	4.9
Osteosarcoma	117	2.9	118	2.6	150	2.9	210	2.7	218	2.7
Ewing's sarcoma	93	2.3	94	2.1	116	2.2	146	1.9	147	1.8
9 Soft-tissue sarcomas	293	7.7	324	7.5	388	7.7	599	7.9	497	6.3
10 Germ cell, trophoblastic and other gonadal neoplasms	130	3.4	145	3.3	201	4.0	256	3.4	251	3.2
11 Carcinoma and other malignant epithelial neoplasms	112	2.8	149	3.4	164	3.2	223	2.9	232	2.9
12 Other and unspecified malignant neoplasms	18	0.5	23	0.5	20	0.4	34	0.4	36	0.5
All cancer	4416	115.9	5041	116.9	5785	114.3	8433	111.5	8648	109.6
All cancer minus leukaemia	2955	77.3	3361	77.7	3897	76.9	5593	73.8	5780	73.1

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.4c Age-standardised rates + (per million) for 1969–1993 for England, Wales and Scotland county districts subdivided into groups using quintiles of population density

Diagnostic group	Group									
	1		2		3		4		5	
	Highest density								Lowest density	
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR
1 Leukaemias	3642	37.0	2581	36.4	1868	38.3	1668	39.4	978	40.0
Lymphoid and unspecified leukaemia	2939	29.9	2085	29.4	1528	31.4	1330	31.5	805	33.0
2 Lyphomas and reticuloendothelial neoplasms	1098	11.1	824	11.3	599	11.9	501	11.5	284	11.2
Hodgkin lymphoma	447	4.5	359	4.9	252	5.0	194	4.4	112	4.3
Non-Hodgkin lymphoma	561	5.7	398	5.5	309	6.2	262	6.1	148	5.9
3 CNS and misc intra-cranial and intra-spinal neoplasms	2480	25.1	1888	26.3	1242	25.2	1175	27.4	689	27.6
Astrocytoma	912	9.2	734	10.2	458	9.3	462	10.8	260	10.4
Primitive neuroectodermal tumours (PNET)	499	5.1	381	5.3	280	5.7	240	5.6	149	6.0
4 Sympathetic nervous system tumours	730	7.5	541	7.7	338	7.1	316	7.6	186	7.8
5 Retinoblastoma	324	3.3	222	3.2	168	3.5	151	3.7	80	3.4
Retinoblastoma - unilateral	204	2.1	129	1.9	94	2.0	104	2.5	52	2.2
Retinoblastoma - bilateral	113	1.2	84	1.2	72	1.5	45	1.1	26	1.1
6 Renal tumours	617	6.3	471	6.7	333	7.0	317	7.6	152	6.4
7 Hepatic tumours	93	0.9	68	1.0	38	0.8	42	1.0	17	0.7
8 Malignant bone tumours	514	5.1	376	5.1	235	4.6	244	5.5	138	5.3
Osteosarcoma	283	2.8	204	2.8	123	2.4	134	3.0	69	2.6
Ewing's sarcoma	203	2.0	137	1.9	100	2.0	94	2.1	62	2.4
9 Soft-tissue sarcomas	664	6.7	551	7.7	366	7.4	330	7.7	190	7.7
10 Germ cell, trophoblastic and other gonadal neoplasms	320	3.2	244	3.4	191	3.9	161	3.8	67	2.7
11 Carcinoma and other malignant epithelial neoplasms	269	2.7	238	3.3	134	2.7	148	3.4	91	3.5
12 Other and unspecified malignant neoplasms	45	0.5	32	0.4	28	0.6	14	0.3	12	0.5
All cancer	10796	109.5	8036	112.6	5540	112.9	5067	118.9	2884	116.6
All cancer minus leukaemia	7154	72.5	5455	76.2	3672	74.7	3399	79.5	1906	76.7

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.4d Age-standardised rates [+] (per million) for 1969–1993 for England, Wales and Scotland county districts grouped according to urban/rural classification

Diagnostic group	Group									
	1		2		3		4		5	
	Most urban								Most rural	
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR
1 Leukaemias	3330	37.0	2560	36.5	2162	37.9	1536	38.8	1149	40.8
Lymphoid and unspecified leukaemia	2682	29.8	2086	29.8	1738	30.5	1238	31.4	943	33.6
2 Lyphomas and reticuloendothelial neoplasms	1015	11.2	797	11.1	689	11.8	461	11.3	344	11.8
Hodgkin lymphoma	406	4.5	356	4.9	286	4.9	167	4.0	149	5.0
Non-Hodgkin lymphoma	528	5.8	381	5.3	346	5.9	251	6.2	172	5.9
3 CNS and misc intra-cranial and intra-spinal neoplasms	2269	25.1	1845	26.0	1498	26.0	1065	26.6	797	27.8
Astrocytoma	844	9.3	693	9.7	568	9.8	415	10.3	306	10.7
Primitive neuroectodermal tumours (PNET)	468	5.2	350	5.0	329	5.7	234	5.9	168	5.9
4 Sympathetic nervous system tumours	665	7.4	512	7.4	440	7.8	283	7.3	211	7.6
5 Retinoblastoma	293	3.3	211	3.1	197	3.5	144	3.8	100	3.7
Retinoblastoma - unilateral	181	2.0	125	1.8	119	2.1	91	2.4	67	2.5
Retinoblastoma - bilateral	105	1.2	77	1.1	76	1.4	51	1.3	31	1.1
6 Renal tumours	580	6.5	429	6.2	410	7.3	287	7.4	184	6.7
7 Hepatic tumours	86	1.0	57	0.8	55	1.0	36	0.9	24	0.9
8 Malignant bone tumours	475	5.2	357	4.9	306	5.2	216	5.2	153	5.1
Osteosarcoma	253	2.8	208	2.9	161	2.7	113	2.7	78	2.6
Ewing's sarcoma	194	2.1	123	1.7	124	2.1	89	2.1	66	2.2
9 Soft-tissue sarcomas	614	6.8	535	7.6	434	7.5	305	7.6	213	7.4
10 Germ cell, trophoblastic and other gonadal neoplasms	296	3.3	245	3.5	216	3.8	127	3.2	99	3.5
11 Carcinoma and other malignant epithelial neoplasms	241	2.6	227	3.1	183	3.1	126	3.1	103	3.5
12 Other and unspecified malignant neoplasms	40	0.4	37	0.5	28	0.5	15	0.4	11	0.4
All cancer	9904	109.8	7812	110.7	6618	115.3	4601	115.5	3388	119.2
All cancer minus leukaemia	6574	72.8	5252	74.2	4456	77.5	3065	76.7	2239	78.4

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.5a Age-standardised rates [+] (per million) for 1969–1993 for England and Wales wards, subdivided in groups using quintiles of the Carstairs index of socio-economic status

Diagnostic group	Groups											
	1		2		3		4		5			
	Least deprived								Most deprived		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	1503	40.8	1490	41.5	1606	39.4	2066	37.2	3046	35.6	***	***
Lymphoid and unspecified leukaemia	1214	33.1	1225	34.2	1325	32.5	1645	29.7	2438	28.5	***	***
2 Lyphomas and reticuloendothelial neoplasms	457	11.7	409	11.0	511	12.2	641	11.4	956	11.2	-	-
Hodgkin lymphoma	181	4.6	162	4.3	202	4.8	263	4.7	410	4.8	-	-
Non-Hodgkin lymphoma	244	6.4	215	5.9	266	6.4	323	5.8	470	5.5	-	*
3 CNS and misc intra-cranial and intra-spinal neoplasms	1070	28.4	985	27.0	1083	26.3	1453	26.0	2157	25.3	*	**
Astrocytoma	408	10.8	376	10.3	380	9.2	545	9.8	819	9.6	-	-
Primitive neuroectodermal tumours (PNET)	236	6.3	192	5.3	216	5.3	300	5.4	421	4.9	-	*
4 Sympathetic nervous system tumours	254	7.1	274	7.8	324	8.1	412	7.5	631	7.4	-	-
5 Retinoblastoma	116	3.3	104	3.0	136	3.4	201	3.7	282	3.3	-	-
Retinoblastoma - unilateral	77	2.2	63	1.8	85	2.1	118	2.1	180	2.1	-	-
Retinoblastoma - bilateral	38	1.1	40	1.2	48	1.2	77	1.4	94	1.1	-	-
6 Renal tumours	275	7.8	246	7.0	261	6.5	396	7.2	533	6.2	-	-
7 Hepatic tumours	36	1.0	29	0.8	32	0.8	55	1.0	83	1.0	-	-
8 Malignant bone tumours	214	5.4	195	5.2	263	6.2	282	5.0	419	4.9	*	*
Osteosarcoma	115	2.9	99	2.6	131	3.1	163	2.9	236	2.8	-	-
Ewing's sarcoma	89	2.3	86	2.3	111	2.6	100	1.8	154	1.8	**	**
9 Soft-tissue sarcomas	280	7.6	274	7.5	347	8.5	417	7.5	591	6.9	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	135	3.6	135	3.7	119	2.9	187	3.3	315	3.7	-	-
11 Carcinoma and other malignant epithelial neoplasms	132	3.4	120	3.2	143	3.4	166	2.9	237	2.8	-	*
12 Other and unspecified malignant neoplasms	20	0.5	23	0.6	12	0.3	26	0.5	37	0.4	-	-
All cancer	4492	120.5	4284	118.4	4837	118.0	6302	113.2	9287	108.6	***	***
All cancer minus leukaemia	2989	79.8	2794	76.9	3231	78.6	4236	76.0	6241	73.0	**	***

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.5b Age-standardised rates [+] (per million) for 1969–1993 for England and Wales wards, subdivided in groups using quintiles of degree of overcrowding

Diagnostic group	Groups											
	1		2		3		4		5			
	Least overcrowded								Most overcrowded		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	1390	41.0	1571	40.5	1627	38.5	1984	37.6	3139	36.1	*	***
Lymphoid and unspecified leukaemia	1134	33.6	1280	33.1	1331	31.6	1603	30.4	2499	28.8	**	***
2 Lyphomas and reticuloendothelial neoplasms	416	11.5	488	12.2	493	11.5	582	10.9	995	11.5	-	-
Hodgkin lymphoma	170	4.6	194	4.8	181	4.2	249	4.6	424	4.9	-	-
Non-Hodgkin lymphoma	219	6.2	253	6.4	261	6.1	301	5.7	484	5.6	-	*
3 CNS and misc intra-cranial and intra-spinal neoplasms	987	28.3	1110	28.2	1089	25.6	1367	25.8	2195	25.3	**	***
Astrocytoma	376	10.7	420	10.6	386	9.1	532	10.0	814	9.4	*	*
Primitive neuroectodermal tumours (PNET)	208	6.0	217	5.6	235	5.5	280	5.3	425	4.9	-	*
4 Sympathetic nervous system tumours	235	7.2	311	8.2	333	8.0	384	7.3	632	7.3	-	-
5 Retinoblastoma	112	3.5	134	3.6	130	3.1	190	3.7	273	3.1	-	-
Retinoblastoma - unilateral	78	2.4	87	2.3	78	1.9	116	2.2	164	1.9	-	-
Retinoblastoma - bilateral	33	1.0	45	1.2	50	1.2	68	1.3	101	1.2	-	-
6 Renal tumours	237	7.3	276	7.3	294	7.0	345	6.6	559	6.4	-	-
7 Hepatic tumours	33	1.0	29	0.8	34	0.8	44	0.8	95	1.1	-	-
8 Malignant bone tumours	193	5.2	235	5.8	237	5.5	286	5.3	422	4.9	-	*
Osteosarcoma	109	2.9	114	2.8	129	3.0	150	2.8	242	2.8	-	-
Ewing's sarcoma	75	2.0	111	2.7	92	2.1	108	2.0	154	1.8	**	**
9 Soft-tissue sarcomas	262	7.6	335	8.6	301	7.1	412	7.8	599	6.9	*	-
10 Germ cell, trophoblastic and other gonadal neoplasms	138	4.0	139	3.5	136	3.2	183	3.5	295	3.4	-	-
11 Carcinoma and other malignant epithelial neoplasms	125	3.4	140	3.5	124	2.9	170	3.2	239	2.8	-	*
12 Other and unspecified malignant neoplasms	21	0.6	18	0.5	20	0.5	22	0.4	37	0.4	-	-
All cancer	4149	120.5	4786	122.4	4818	113.6	5969	112.8	9480	109.2	***	***
All cancer minus leukaemia	2759	79.5	3215	81.9	3191	75.1	3985	75.2	6341	73.1	***	***

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.5c Age-standardised rates [+] (per million) for 1969–1993 for England and Wales wards, subdivided in groups using quintiles of population density

Diagnostic group	Groups											
	1		2		3		4		5			
	Highest density								Lowest density		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	3188	37.4	2734	38.1	2029	38.2	1152	38.9	608	40.7	-	-
Lymphoid and unspecified leukaemia	2571	30.2	2217	31.0	1597	30.2	965	32.6	497	33.4	-	-
2 Lyphomas and reticuloendothelial neoplasms	1011	11.9	828	11.3	605	11.1	353	11.5	177	11.2	-	-
Hodgkin lymphoma	423	5.0	335	4.5	240	4.4	151	4.9	69	4.2	-	-
Non-Hodgkin lymphoma	503	5.9	423	5.8	320	5.9	177	5.8	95	6.1	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	2095	24.6	1997	27.6	1428	26.6	792	26.3	436	28.3	**	*
Astrocytoma	769	9.0	754	10.4	524	9.7	314	10.4	167	10.8	*	*
Primitive neuroectodermal tumours (PNET)	416	4.9	385	5.3	317	5.9	169	5.6	78	5.1	-	-
4 Sympathetic nervous system tumours	625	7.3	534	7.5	385	7.4	244	8.4	107	7.4	-	-
5 Retinoblastoma	272	3.2	274	3.9	160	3.1	91	3.2	42	3.0	-	-
Retinoblastoma - unilateral	172	2.0	162	2.3	107	2.1	54	1.9	28	2.0	-	-
Retinoblastoma - bilateral	97	1.1	102	1.5	48	0.9	36	1.3	14	1.0	-	-
6 Renal tumours	540	6.3	490	6.9	354	6.8	219	7.6	108	7.5	-	-
7 Hepatic tumours	83	1.0	72	1.0	47	0.9	20	0.7	13	0.9	-	-
8 Malignant bone tumours	425	5.0	394	5.3	293	5.3	174	5.6	87	5.3	-	-
Osteosarcoma	240	2.8	215	2.9	146	2.6	95	3.0	48	2.9	-	-
Ewing's sarcoma	154	1.8	153	2.1	131	2.4	67	2.1	35	2.2	-	*
9 Soft-tissue sarcomas	579	6.8	539	7.5	441	8.3	229	7.6	121	7.9	-	*
10 Germ cell, trophoblastic and other gonadal neoplasms	288	3.4	257	3.6	192	3.6	104	3.5	50	3.3	-	-
11 Carcinoma and other malignant epithelial neoplasms	265	3.1	209	2.8	166	3.0	98	3.2	60	3.7	-	-
12 Other and unspecified malignant neoplasms	42	0.5	31	0.4	24	0.5	14	0.5	7	0.5	-	-
All cancer	9413	110.5	8359	116.1	6124	114.7	3490	116.9	1816	119.8	*	**
All cancer minus leukaemia	6225	73.1	5625	78.0	4095	76.5	2338	77.9	1208	79.1	**	**

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.5d Age-standardised rates [+] (per million) for 1969–1993 for England and Wales wards, grouped according to urban/rural classifications

Diagnostic group	Classification												p # hetero	p ++ trend
	1		2		3		4		5		6			
	Most urban										Most rural			
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	6735	37.9	1718	38.0	394	37.0	157	43.6	57	37.7	650	40.4	-	-
Lymphoid and unspecified leukaemia	5444	30.7	1358	30.1	326	30.7	127	35.4	52	34.3	540	33.7	-	-
2 Lyphomas and reticuloendothelial neoplasms	2096	11.7	502	10.9	123	11.2	43	11.5	15	9.4	195	11.4	-	-
Hodgkin lymphoma	848	4.7	221	4.7	53	4.8	13	3.4	8	5.0	75	4.3	-	-
Non-Hodgkin lymphoma	1072	6.0	249	5.4	58	5.3	24	6.4	7	4.4	108	6.4	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	4659	26.1	1218	26.7	279	25.8	86	23.4	53	34.5	453	27.4	-	-
Astrocytoma	1711	9.6	464	10.1	119	11.0	33	9.0	24	15.7	177	10.6	-	-
Primitive neuroectodermal tumours (PNET)	909	5.1	279	6.1	62	5.8	21	5.7	8	5.2	86	5.3	-	-
4 Sympathetic nervous system tumours	1304	7.4	349	7.8	93	8.9	17	4.8	12	8.1	120	7.7	-	-
5 Retinoblastoma	589	3.4	152	3.4	38	3.7	12	3.4	4	2.8	44	2.9	-	-
Retinoblastoma – unilateral	369	2.1	88	2.0	24	2.3	10	2.9	2	1.4	30	2.0	-	-
Retinoblastoma – bilateral	203	1.2	63	1.4	13	1.3	2	0.6	2	1.4	14	0.9	-	-
6 Renal tumours	1157	6.6	308	6.9	83	7.9	37	10.5	16	10.8	110	7.2	-	-
7 Hepatic tumours	172	1.0	36	0.8	11	1.0	3	0.8	2	1.4	11	0.7	-	-
8 Malignant bone tumours	933	5.2	252	5.4	63	5.7	27	7.1	5	3.1	93	5.3	-	-
Osteosarcoma	507	2.8	135	2.9	32	2.9	14	3.6	4	2.4	52	2.9	-	-
Ewing's sarcoma	364	2.0	103	2.2	27	2.4	10	2.6	0	0.0	36	2.1	-	-
9 Soft-tissue sarcomas	1285	7.2	368	8.1	83	7.8	26	7.1	15	9.8	132	8.1	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	620	3.5	158	3.5	36	3.4	18	4.9	7	4.6	52	3.2	-	-
11 Carcinoma and other malignant epithelial neoplasms	557	3.1	129	2.8	35	3.1	14	3.7	3	1.9	60	3.5	-	-
12 Other and unspecified malignant neoplasms	83	0.5	20	0.4	5	0.5	1	0.3	1	0.7	8	0.5	-	-
All cancer	20190	113.4	5210	114.7	1243	115.9	441	121.1	190	124.8	1928	118.2	-	-
All cancer minus leukaemia	13455	75.5	3492	76.7	849	79.0	284	77.5	133	87.1	1278	77.8	-	-

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.6a Age-standardised rates + (per million) for 1969–1993 for Scottish wards, subdivided in groups using quintiles of the Carstairs index of socio-economic status

Diagnostic group	Groups											
	1		2		3		4		5			
	Least deprived								Most deprived		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	177	42.4	166	45.9	148	36.8	234	35.9	301	33.2	**	***
Lymphoid and unspecified leukaemia	150	36.0	137	38.0	122	30.4	193	29.7	238	26.4	**	***
2 Lyphomas and reticuloendothelial neoplasms	70	15.8	44	11.8	41	9.8	76	11.2	101	10.7	-	*
Hodgkin lymphoma	31	6.9	15	4.0	17	4.0	39	5.7	44	4.6	-	-
Non-Hodgkin lymphoma	35	8.0	22	5.9	21	5.1	31	4.7	51	5.4	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	120	28.0	105	28.6	121	29.7	174	26.3	206	22.3	-	*
Astrocytoma	45	10.6	49	13.3	45	11.0	69	10.5	90	9.7	-	-
Primitive neuroectodermal tumours (PNET)	31	7.2	22	6.0	33	8.1	45	6.9	53	5.8	-	-
4 Sympathetic nervous system tumours	44	10.6	29	8.2	29	7.4	56	8.8	58	6.5	-	*
5 Retinoblastoma	16	4.0	12	3.4	19	4.9	27	4.3	32	3.7	-	-
Retinoblastoma - unilateral	8	2.0	4	1.1	9	2.3	18	2.8	21	2.4	-	-
Retinoblastoma - bilateral	7	1.7	8	2.3	9	2.3	9	1.4	10	1.1	-	-
6 Renal tumours	25	6.1	23	6.5	17	4.3	47	7.4	67	7.5	-	-
7 Hepatic tumours	3	0.7	4	1.2	5	1.3	3	0.5	8	0.9	-	-
8 Malignant bone tumours	21	4.7	10	2.6	23	5.4	36	5.3	44	4.6	-	-
Osteosarcoma	9	2.0	4	1.0	11	2.6	24	3.5	21	2.2	-	-
Ewing's sarcoma	11	2.4	4	1.0	10	2.4	11	1.6	20	2.1	-	-
9 Soft-tissue sarcomas	33	7.7	23	6.2	29	7.1	46	7.0	61	6.6	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	13	3.0	12	3.2	18	4.3	14	2.1	35	3.8	-	-
11 Carcinoma and other malignant epithelial neoplasms	14	3.1	11	2.9	10	2.4	20	2.9	27	2.9	-	-
12 Other and unspecified malignant neoplasms	2	0.5	0	0.0	2	0.5	4	0.6	5	0.5	-	-
All cancer	538	126.4	439	120.5	462	114.0	737	112.2	945	103.1	**	***
All cancer minus leukaemia	361	84.0	273	74.5	314	77.2	503	76.3	644	69.9	-	*

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.6b Age-standardised rates [+] (per million) for 1969–1993 for Scottish wards, subdivided in groups using quintiles of degree of overcrowding

Diagnostic group	Groups											
	1		2		3		4		5			
	Least overcrowded								Most overcrowded		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	132	39.6	190	47.5	171	39.0	224	36.0	309	32.7	**	***
Lymphoid and unspecified leukaemia	109	32.8	163	40.8	136	31.1	184	29.6	248	26.4	***	***
2 Lyphomas and reticuloendothelial neoplasms	46	13.0	57	13.7	55	12.2	87	13.4	87	8.8	*	*
Hodgkin lymphoma	19	5.3	24	5.7	25	5.5	40	6.1	38	3.8	-	-
Non-Hodgkin lymphoma	25	7.1	25	6.1	26	5.8	41	6.4	43	4.4	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	91	26.6	129	31.8	118	26.6	172	27.1	216	22.5	*	*
Astrocytoma	41	12.1	54	13.2	46	10.4	66	10.4	91	9.4	-	-
Primitive neuroectodermal tumours (PNET)	23	6.7	34	8.4	21	4.8	44	6.9	62	6.5	-	-
4 Sympathetic nervous system tumours	33	9.9	32	8.1	36	8.4	52	8.6	63	6.8	-	-
5 Retinoblastoma	16	5.0	12	3.1	17	4.0	32	5.3	29	3.2	-	-
Retinoblastoma - unilateral	6	1.8	6	1.5	10	2.4	18	3.0	20	2.2	-	-
Retinoblastoma - bilateral	10	3.1	4	1.0	7	1.6	13	2.2	9	1.0	-	-
6 Renal tumours	23	7.1	24	6.1	21	4.9	40	6.5	71	7.7	-	-
7 Hepatic tumours	2	0.6	5	1.3	3	0.7	7	1.1	6	0.7	-	-
8 Malignant bone tumours	11	3.1	26	6.2	18	4.0	27	4.1	52	5.2	-	-
Osteosarcoma	5	1.4	11	2.6	13	2.9	12	1.8	28	2.8	-	-
Ewing's sarcoma	6	1.7	12	2.9	4	0.9	13	2.0	21	2.1	-	-
9 Soft-tissue sarcomas	25	7.2	33	8.1	32	7.3	42	6.6	60	6.3	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	11	3.1	17	4.2	12	2.7	17	2.7	35	3.6	-	-
11 Carcinoma and other malignant epithelial neoplasms	13	3.5	11	2.6	11	2.4	18	2.7	29	3.0	-	-
12 Other and unspecified malignant neoplasms	2	0.6	2	0.5	1	0.2	2	0.3	6	0.6	-	-
All cancer	405	119.3	538	133	495	112.4	720	114.2	963	101.0	***	***
All cancer minus leukaemia	273	79.7	348	85.5	324	73.4	496	78.3	654	68.3	**	**

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.6c Age-standardised rates [+] (per million) for 1969–1993 for Scottish wards, subdivided in groups using quintiles of population density

Diagnostic group	Groups											
	1		2		3		4		5			
	Highest density								Lowest density		p # hetero	p ++ trend
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	348	35.5	281	35.3	192	36.9	148	46.9	57	45.0	*	**
Lymphoid and unspecified leukaemia	275	28.3	234	29.5	167	32.1	117	37.2	47	37.1	-	**
2 Lyphomas and reticuloendothelial neoplasms	106	10.4	114	13.6	48	8.9	43	13.1	21	15.6	*	-
Hodgkin lymphoma	42	4.1	55	6.5	22	4.0	17	5.1	10	7.1	-	-
Non-Hodgkin lymphoma	54	5.3	55	6.6	21	3.9	21	6.4	9	6.8	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	239	24.0	208	25.5	148	27.9	91	28.6	40	30.7	-	*
Astrocytoma	103	10.3	86	10.5	53	10.0	36	11.2	20	15.2	-	-
Primitive neuroectodermal tumours (PNET)	62	6.3	50	6.2	40	7.6	25	7.9	7	5.3	-	-
4 Sympathetic nervous system tumours	76	7.9	58	7.4	48	9.4	23	7.4	11	8.7	-	-
5 Retinoblastoma	37	3.9	38	4.9	13	2.6	16	5.2	2	1.7	-	-
Retinoblastoma - unilateral	19	2.0	19	2.5	9	1.8	12	3.9	1	0.8	-	-
Retinoblastoma - bilateral	16	1.7	18	2.4	4	0.8	4	1.3	1	0.8	-	-
6 Renal tumours	68	7.1	61	7.8	24	4.7	20	6.4	6	5.0	-	-
7 Hepatic tumours	9	0.9	6	0.8	3	0.6	4	1.3	1	0.8	-	-
8 Malignant bone tumours	54	5.2	34	4.0	31	5.7	11	3.2	4	2.9	-	-
Osteosarcoma	26	2.5	20	2.4	16	2.9	5	1.5	2	1.5	-	-
Ewing's sarcoma	24	2.3	12	1.4	14	2.6	4	1.2	2	1.4	-	-
9 Soft-tissue sarcomas	77	7.8	52	6.4	31	5.9	24	7.5	8	5.8	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	31	3.1	39	4.8	9	1.7	9	2.8	4	3.1	*	-
11 Carcinoma and other malignant epithelial neoplasms	30	2.9	24	2.9	13	2.4	12	3.6	3	2.1	-	-
12 Other and unspecified malignant neoplasms	4	0.4	4	0.5	4	0.8	1	0.3	0	0.0	-	-
All cancer	1079	109.2	919	113.9	564	107.3	402	126.4	157	121.4	-	-
All cancer minus leukaemia	731	73.7	638	78.6	372	70.4	254	79.4	100	76.3	-	-

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.6d Age-standardised rates [+] (per million) for 1969–1993 for Scottish wards, grouped according to urban/rural classifications

Diagnostic group	Classification										p # hetero	p ++ trend
	1		2		3		4		5			
	Most urban								Most rural			
	No	ASR	No	ASR	No	ASR	No	ASR	No	ASR		
1 Leukaemias	221	33.2	181	35.4	295	36.8	238	41.0	91	50.2	*	***
Lymphoid and unspecified leukaemia	183	27.6	143	28.1	236	29.6	204	35.1	74	41.0	*	***
2 Lyphomas and reticuloendothelial neoplasms	72	10.4	67	12.5	95	11.3	72	11.9	26	13.7	-	-
Hodgkin lymphoma	28	4.0	23	4.3	54	6.4	28	4.5	13	6.7	-	-
Non-Hodgkin lymphoma	39	5.6	37	6.9	37	4.5	37	6.2	10	5.3	-	-
3 CNS and misc intra-cranial and intra-spinal neoplasms	156	22.9	152	29.3	199	24.5	170	28.7	49	27.0	-	-
Astrocytoma	70	10.2	68	13.1	75	9.2	62	10.4	23	12.5	-	-
Primitive neuroectodermal tumours (PNET)	37	5.4	45	8.7	45	5.6	46	7.8	11	6.1	-	-
4 Sympathetic nervous system tumours	52	8.0	47	9.3	58	7.4	44	7.8	15	8.2	-	-
5 Retinoblastoma	22	3.4	15	3.0	43	5.5	21	3.8	5	2.9	-	-
Retinoblastoma – unilateral	11	1.7	8	1.6	22	2.8	15	2.7	4	2.3	-	-
Retinoblastoma – bilateral	10	1.6	6	1.2	20	2.6	6	1.1	1	0.6	-	-
6 Renal tumours	48	7.3	41	8.2	48	6.1	33	5.8	9	5.1	-	-
7 Hepatic tumours	5	0.8	3	0.6	8	1.0	6	1.0	1	0.6	-	-
8 Malignant bone tumours	29	4.1	27	5.0	44	5.2	30	4.8	4	2.0	-	-
Osteosarcoma	16	2.2	15	2.8	19	2.2	18	2.9	1	0.5	-	-
Ewing's sarcoma	11	1.6	10	1.9	23	2.8	10	1.6	2	1.0	-	-
9 Soft-tissue sarcomas	48	7.1	44	8.5	48	5.9	39	6.6	13	6.8	-	-
10 Germ cell, trophoblastic and other gonadal neoplasms	26	3.8	14	2.6	33	4.1	14	2.4	5	2.7	-	-
11 Carcinoma and other malignant epithelial neoplasms	19	2.7	17	3.2	24	2.9	18	2.9	4	2.0	-	-
12 Other and unspecified malignant neoplasms	4	0.6	2	0.4	3	0.4	4	0.7	0	0.0	-	-
All cancer	702	104.4	610	117.9	898	111.2	689	117.4	222	121.1	-	*
All cancer minus leukaemia	481	71.1	429	82.6	603	74.3	451	76.4	131	70.9	-	-

+ Age-standardised rate. This is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Significance test for group differences in crude incidence rates. ++ Significance test for trend in crude incidence rates.

* $p<0.05$ ** $p<0.01$ *** $p<0.001$ - non-significant

Table 3.7 Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(a) Leukaemias

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	36.9	35.4	0.0
2	36.7	38.2	37.2
3 Lowest density	0.0	5.5	40.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	39.0	40.7	40.1
2	37.3	37.4	38.2
3 Most deprived	36.2	35.6	42.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	38.9	40.3	40.6
2	37.9	36.1	39.3
3 Most deprived	36.1	35.8	39.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	38.2	38.7	39.5
2	36.6	37.6	41.5
3 Most overcrowded	36.9	35.9	39.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	37.4	38.9	39.5
2	36.5	38.6	39.2
3 Most overcrowded	36.8	36.1	41.8

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.7 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(b) CNS and miscellaneous intra-cranial and intra-spinal neoplasms

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	25.6	26.3	0.0
2	24.9	25.7	26.7
3 Lowest density	0.0	28.7	27.2

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	25.5	26.1	27.6
2	25.9	26.5	27.3
3 Most deprived	25.6	24.9	27.3

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	25.5	26.1	27.7
2	25.9	26.7	26.8
3 Most deprived	25.4	25.5	26.4

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	27.5	26.8	27.7
2	27.2	25.3	26.7
3 Most overcrowded	24.6	26.1	26.5

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	27.5	26.5	28.0
2	27.1	25.3	26.4
3 Most overcrowded	24.9	25.2	27.4

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.7 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(c) All cancer minus leukaemia

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	73.2	77.7	0.0
2	74.0	75.7	77.2
3 Lowest density	0.0	83.2	77.9

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	75.0	76.3	79.8
2	75.3	75.7	79.1
3 Most deprived	72.8	75.0	74.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	74.5	76.6	79.9
2	74.7	78.0	76.9
3 Most deprived	72.5	75.5	75.2

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	77.4	76.2	79.1
2	76.0	76.7	78.8
3 Most overcrowded	71.8	77.1	75.0

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	78.9	75.6	79.2
2	76.4	75.1	80.7
3 Most overcrowded	72.1	76.4	74.6

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.7 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(d) Lymphoid leukaemia plus unspecified leukaemia

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	29.8	28.7	0.0
2	29.8	31.0	30.8
3 Lowest density	0.0	28.5	33.1

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	30.9	32.7	32.1
2	30.5	30.7	31.8
3 Most deprived	29.2	29.2	34.4

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	30.8	32.5	32.4
2	31.0	29.5	32.9
3 Most deprived	29.2	29.0	32.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	30.4	31.2	31.8
2	30.0	30.8	34.1
3 Most overcrowded	29.7	28.8	33.0

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	29.5	31.2	32.0
2	29.8	31.8	32.0
3 Most overcrowded	29.7	29.4	33.8

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.7 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(e) Non-Hodgkin lymphoma

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	5.6	5.8	0.0
2	5.1	6.1	5.2
3 Lowest density	0.0	5.8	6.0

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	6.2	6.0	6.7
2	5.7	5.8	5.0
3 Most deprived	5.5	6.0	6.1

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	5.9	6.2	6.8
2	5.8	5.5	5.2
3 Most deprived	5.5	6.4	5.1

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	6.0	6.2	6.5
2	5.9	5.6	5.3
3 Most overcrowded	5.4	6.5	5.3

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	6.4	6.4	6.1
2	5.8	5.5	5.6
3 Most overcrowded	5.5	5.8	6.3

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.7 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England, Wales and Scotland county districts subdivided by tertiles of socio-economic status, degree of overcrowding, population density and urban/rural status

(f) All cancer

Age-standardised rate + (per million) analysing tertiles of urban/rural status and population density simultaneously

Population density	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Highest density	110.1	113.1	0.0
2	110.7	113.8	114.4
3 Lowest density	0.0	118.7	118.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	114.0	117.0	119.8
2	112.5	113.1	117.3
3 Most deprived	109.0	110.6	117.7

Age-standardised rate + (per million) analysing tertiles of socio-economic status and urban/rural status simultaneously

Socio-economic status	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least deprived	113.4	116.9	120.5
2	112.6	114.1	116.2
3 Most deprived	108.6	111.3	115.1

Age-standardised rate + (per million) analysing tertiles of overcrowding and urban/rural status simultaneously

Overcrowding	**Urban/rural status**		
	1	**2**	**3**
	Most urban		**Most rural**
1 Least overcrowded	115.6	114.9	118.6
2	112.6	114.3	120.3
3 Most overcrowded	108.6	113.0	114.8

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	116.3	114.4	118.8
2	112.8	113.7	119.8
3 Most overcrowded	108.9	112.5	116.4

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(a) Leukaemias

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Highest density	38.0	36.0	27.7	0.0	0.0	84.8
2	38.1	38.0	38.7	33.8	0.0	41.5
3 Lowest density	30.9	42.6	35.9	45.6	41.2	40.3

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	42.8	40.1	41.0
2	40.6	39.5	39.6
3 Most deprived	36.0	34.9	34.2

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least deprived	41.5	41.3	33.8	45.6	48.5	41.9
2	40.1	39.9	42.2	43.9	20.8	38.8
3 Most deprived	36.0	34.2	36.5	33.6	11.8	38.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least overcrowded	41.1	39.3	35.6	39.1	45.7	40.5
2	37.7	39.3	36.3	46.2	31.5	40.6
3 Most overcrowded	37.0	36.0	40.8	43.8	29.0	39.6

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	41.6	39.2	40.8
2	37.8	38.6	39.0
3 Most overcrowded	37.1	36.4	39.6

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(b) CNS and miscellaneous intra-cranial and intra-spinal neoplasms

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Highest density	25.7	27.4	37.3	0.0	129.5	0.0
2	27.0	26.1	22.7	15.2	17.2	43.0
3 Lowest density	31.3	29.4	27.9	24.9	35.4	26.9

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	26.9	27.6	28.3
2	25.6	27.5	27.3
3 Most deprived	25.7	24.5	27.0

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least deprived	27.8	27.4	26.2	26.9	35.0	27.3
2	26.2	28.0	27.2	21.4	39.7	27.2
3 Most deprived	25.6	25.2	22.3	15.5	0.0	28.6

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least overcrowded	28.7	28.4	25.1	28.6	35.7	29.5
2	25.7	26.8	26.9	18.5	34.9	25.7
3 Most overcrowded	25.5	25.3	25.1	27.0	28.8	25.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	28.4	28.4	28.9
2	26.2	25.5	26.2
3 Most overcrowded	25.2	25.6	29.2

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(c) All cancer minus leukaemia

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Highest density	74.5	78.8	74.7	0.0	335.8	156.8
2	77.7	75.6	72.7	72.7	69.6	92.1
3 Lowest density	82.9	81.0	83.3	78.5	87.3	77.2

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	77.3	77.7	79.2
2	75.9	79.9	81.0
3 Most deprived	74.0	73.0	76.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least deprived	77.5	78.9	76.3	83.5	89.4	77.1
2	77.3	80.0	88.8	71.6	89.5	78.2
3 Most deprived	74.1	72.6	68.9	74.7	48.2	80.2

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least overcrowded	80.0	82.9	79.6	79.2	91.7	80.9
2	75.5	75.4	82.3	70.6	81.7	75.7
3 Most overcrowded	74.0	73.2	71.1	93.2	86.7	74.4

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	79.9	80.1	83.5
2	75.8	75.6	76.2
3 Most overcrowded	73.5	74.5	79.0

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(d) Lymphoid leukaemia plus unspecified leukaemia

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Highest density	30.6	28.8	27.7	0.0	0.0	84.8
2	31.1	29.9	31.4	30.5	0.0	35.2
3 Lowest density	25.8	34.8	30.2	36.5	37.4	33.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	34.4	31.9	34.8
2	32.7	33.1	32.4
3 Most deprived	29.1	27.5	27.2

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least deprived	33.3	32.6	28.8	38.9	44.2	35.3
2	33.0	32.4	34.8	34.1	18.5	32.0
3 Most deprived	29.0	26.6	28.4	25.8	11.8	32.3

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least overcrowded	33.2	32.1	30.5	30.5	41.3	34.7
2	30.8	31.0	30.8	40.5	29.7	32.7
3 Most overcrowded	29.8	27.9	30.5	30.2	24.1	33.7

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	33.3	32.0	34.5
2	30.3	31.6	32.4
3 Most overcrowded	30.0	28.4	31.4

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(e) Non-Hodgkin lymphoma

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Highest density	6.0	5.0	0.0	0.0	0.0	0.0
2	6.1	5.6	3.0	5.1	17.7	8.3
3 Lowest density	5.2	5.1	7.0	6.7	3.4	6.4

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	5.5	6.0	6.6
2	6.7	6.0	5.5
3 Most deprived	5.7	5.4	6.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least deprived	5.9	5.8	4.6	8.5	4.1	7.2
2	6.5	5.9	6.4	3.8	3.8	5.0
3 Most deprived	5.8	4.8	5.6	7.7	11.8	8.6

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**					
	1	**2**	**3**	**4**	**5**	**6**
	Most urban					**Most rural**
1 Least overcrowded	6.5	6.3	4.2	7.2	1.4	7.1
2	6.3	4.9	6.7	5.5	7.8	6.2
3 Most overcrowded	5.7	5.1	4.9	7.5	4.6	5.0

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	6.3	6.2	6.6
2	6.4	5.6	6.1
3 Most overcrowded	5.6	5.5	5.1

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.8 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 England and Wales wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(f) All cancer

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	Urban/rural category					
	1	2	3	4	5	6
	Most urban					Most rural
1 Highest density	112.5	114.8	102.3	0.0	335.8	241.6
2	115.8	113.5	111.4	106.5	69.6	133.6
3 Lowest density	113.8	123.6	119.1	124.1	128.5	117.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	Population density		
	1	2	3
	Highest density		Lowest density
1 Least deprived	120.1	117.8	120.2
2	116.5	119.4	120.6
3 Most deprived	110.1	107.9	110.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	Urban/rural category					
	1	2	3	4	5	6
	Most urban					Most rural
1 Least deprived	119.0	120.2	110.2	129.1	137.9	118.9
2	117.4	119.9	130.9	115.5	110.3	116.9
3 Most deprived	110.0	106.8	105.4	108.3	60.0	119.1

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	Urban/rural category					
	1	2	3	4	5	6
	Most urban					Most rural
1 Least overcrowded	121.1	122.2	115.3	118.3	137.4	121.4
2	113.1	114.6	118.7	116.8	113.2	116.3
3 Most overcrowded	110.9	109.3	111.9	137.0	115.7	114.0

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	Population density		
	1	2	3
	Highest density		Lowest density
1 Least overcrowded	121.6	119.3	124.2
2	113.6	114.1	115.2
3 Most overcrowded	110.5	110.9	118.6

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.9 Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(a) Leukaemias

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	34.0	35.9	36.5	35.2	0.0
2	23.3	32.5	38.5	42.3	24.7
3 Lowest density	0.0	0.0	20.0	38.2	55.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	36.9	43.5	48.2
2	41.3	37.6	45.1
3 Most deprived	33.5	34.4	36.5

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	41.7	27.3	47.5	45.1	47.1
2	46.5	46.9	31.5	43.6	54.9
3 Most deprived	30.1	36.3	36.9	30.6	56.2

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	47.6	28.2	44.8	45.8	53.4
2	32.8	38.5	36.5	42.4	46.7
3 Most overcrowded	30.7	37.4	34.5	33.4	48.9

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	40.1	40.3	55.7
2	36.5	40.6	43.9
3 Most overcrowded	33.7	35.3	26.2

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.9 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(b) CNS and miscellaneous intra-cranial and intra-spinal neoplasms

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	22.9	30.2	24.0	24.6	0.0
2	22.0	24.2	24.1	29.2	24.9
3 Lowest density	0.0	0.0	38.9	27.9	27.4

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	32.8	24.4	26.4
2	28.9	30.8	30.2
3 Most deprived	22.6	23.5	29.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	28.8	34.9	27.9	27.2	21.4
2	38.6	32.5	26.8	31.0	30.4
3 Most deprived	20.0	26.2	21.7	27.1	56.8

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	25.1	33.3	33.9	26.1	24.1
2	40.9	27.7	21.7	32.6	29.5
3 Most overcrowded	19.7	28.1	23.1	26.4	32.6

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	30.1	28.1	27.3
2	30.5	26.9	28.6
3 Most overcrowded	22.5	24.9	30.0

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.9 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(c) All cancer minus leukaemia

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	70.2	85.6	73.8	66.7	0.0
2	80.3	65.3	74.0	73.4	61.8
3 Lowest density	#	0.0	92.5	86.0	72.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	85.6	74.3	75.0
2	86.3	71.6	83.2
3 Most deprived	70.4	72.6	90.8

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	83.4	99.4	72.0	72.5	70.6
2	93.8	84.4	78.1	78.3	66.4
3 Most deprived	66.2	75.0	72.5	78.9	92.4

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	79.1	96.6	86.9	74.5	70.5
2	97.3	80.2	68.8	81.4	73.7
3 Most overcrowded	65.6	77.7	73.6	71.6	57.2

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	84.8	80.6	76.8
2	82.5	68.9	85.8
3 Most overcrowded	71.1	70.4	78.5

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.
# This category had one recorded case, but no population denominator.

Table 3.9 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(d) Lymphoid leukaemia plus unspecified leukaemia

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	28.3	27.8	30.2	35.2	0.0
2	19.1	30.1	29.5	37.5	18.6
3 Lowest density	0.0	0.0	15.0	28.7	45.9

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	29.9	38.1	39.5
2	36.2	31.6	33.0
3 Most deprived	26.9	27.7	32.0

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	33.0	21.4	40.8	39.8	38.2
2	37.3	40.2	27.8	35.0	42.8
3 Most deprived	25.5	28.4	27.0	28.4	56.2

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	38.6	23.4	38.1	40.6	43.6
2	28.9	27.6	30.8	34.0	39.2
3 Most overcrowded	25.5	30.2	26.1	30.3	33.3

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	33.0	36.2	45.5
2	30.4	33.8	32.8
3 Most overcrowded	27.3	28.5	21.6

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.9 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(e) Non-Hodgkin lymphoma

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	5.5	8.0	5.2	8.9	0.0
2	8.0	1.2	3.0	5.7	6.1
3 Lowest density	0.0	0.0	9.6	7.1	5.1

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	8.4	5.7	5.9
2	5.9	4.7	6.1
3 Most deprived	5.6	3.1	8.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	7.2	11.4	3.7	6.6	5.1
2	5.5	7.2	4.3	6.1	5.1
3 Most deprived	5.3	5.0	4.8	5.8	7.3

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	7.4	12.7	3.0	6.5	6.4
2	3.7	5.4	6.0	5.6	4.9
3 Most overcrowded	5.6	5.1	4.1	6.6	0.0

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	9.1	5.3	6.5
2	6.4	4.6	4.8
3 Most overcrowded	5.3	3.9	8.9

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

Table 3.9 Continued

Age-standardised rates (per million) age 0–14 years for 1969–1993 Scottish wards subdivided by tertiles of socio-economic status, degree of overcrowding and population density and by categories of urban/rural classification

(f) All cancer

Age-standardised rate + (per million) analysing categories of urban/rural classification and tertiles of population density simultaneously

Population density	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Highest density	104.2	121.5	110.2	101.9	0.0
2	103.6	97.8	112.5	115.7	86.5
3 Lowest density	#	0.0	112.4	124.2	128.6

Age-standardised rate + (per million) analysing tertiles of socio-economic status and population density simultaneously

Socio-economic status	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least deprived	122.5	117.8	123.3
2	127.6	109.2	128.3
3 Most deprived	104.0	107.0	127.3

Age-standardised rate + (per million) analysing tertiles of socio-economic status and categories of urban/rural classification simultaneously

Socio-economic status	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least deprived	125.1	126.8	119.4	117.6	117.6
2	140.2	131.3	109.6	121.8	121.2
3 Most deprived	96.3	111.2	109.4	109.5	148.5

Age-standardised rate + (per million) analysing tertiles of overcrowding and categories of urban/rural classification simultaneously

Overcrowding	**Urban/rural category**				
	1	**2**	**3**	**4**	**5**
	Most urban				**Most rural**
1 Least overcrowded	126.8	124.9	131.7	120.3	123.9
2	130.0	118.7	105.2	123.8	120.4
3 Most overcrowded	96.4	115.1	108.0	105.0	106.1

Age-standardised rate + (per million) analysing tertiles of overcrowding and population density simultaneously

Overcrowding	**Population density**		
	1	**2**	**3**
	Highest density		**Lowest density**
1 Least overcrowded	124.9	120.9	132.5
2	119.1	109.5	129.7
3 Most overcrowded	104.8	105.7	104.7

+ The age-standardised rate is the rate for ages 0–14 years standardised according to a uniform age distribution, ie the rate obtained by averaging the age-specific rates weighted as though there were equal numbers of children in each five year age group.

This category had one recorded case but no population denominator.

Table 3.10 England and Wales, Census Wards. Regression analyses of crude incidence rates at ages 0–14 years for groups of wards categorised according to values of specified factors

The following table shows, for each diagnostic group, the relative risks at each level of three socio-demographic factors and also the values having allowed separately for each of the other factors and for region. (There are no joint analyses for socio-economic score and overcrowding because these two variables are closely correlated.) The possible effect of each factor, and whether there is a trend in the effect related to the level of the factor, is indicated by the significance test shown in the last two columns. The tests for each variable, without allowing for any of the others, are the same as those in Table 3.5.

* p<0.05 ** p<0.01 *** p<0.001 - non-significant

Table 3.10(a)

Leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						<0.001	***		
+ Socio-economic score	Least deprived	1.03	0.98	0.94	0.92	0.004	**	<0.001	***
+ Overcrowding	Least overcrowded	1.01	0.97	0.96	0.93	0.082	-	0.006	**
+ Population density	Highest density	1.01	1.02	1.02	1.05	0.899	-	0.368	-
Socio-economic score	Least deprived	1.03	0.98	0.93	0.90	<0.001	***	<0.001	***
+ Region						0.025	*		
+ Population density	Highest density	0.98	0.96	0.95	0.97	0.553	-	0.136	-
Overcrowding	Least overcrowded	1.01	0.96	0.94	0.92	0.010	*	<0.001	***
+ Region						0.005	**		
+ Population density	Highest density	0.98	0.97	0.97	1.00	0.839	-	0.539	-
Population density	Highest density	1.01	1.01	1.02	1.05	0.846	-	0.320	-
+ Region						<0.001	***		
+ Socio-economic score	Least deprived	1.03	0.97	0.92	0.88	<0.001	***	<0.001	***
+ Overcrowding	Least overcrowded	1.01	0.96	0.94	0.90	0.010	*	<0.001	***

Lymphoid and unspecified leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.001	**		
+ Socio-economic score	Least deprived	1.05	1.00	0.93	0.91	<0.001	***	<0.001	***
+ Overcrowding	Least overcrowded	1.01	0.97	0.95	0.91	0.020	*	0.001	**
+ Population density	Highest density	1.02	0.99	1.05	1.05	0.514	-	0.295	-
Socio-economic score	Least deprived	1.05	1.00	0.92	0.89	<0.001	***	<0.001	***
+ Region						0.026	*		
+ Population density	Highest density	0.98	0.93	0.97	0.96	0.283	-	0.192	-
Overcrowding	Least overcrowded	1.01	0.97	0.94	0.89	0.002	**	<0.001	***
+ Region						0.009	**		
+ Population density	Highest density	0.98	0.94	0.99	1.00	0.320	-	0.593	-
Population density	Highest density	1.01	0.98	1.06	1.07	0.288	-	0.181	-
+ Region						0.002	**		
+ Socio-economic score	Least deprived	1.04	0.99	0.91	0.87	<0.001	***	<0.001	***
+ Overcrowding	Least overcrowded	1.00	0.96	0.93	0.88	0.002	**	<0.001	***

Table 3.10(b)

Lymphomas and reticuloendothelial neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.274	-		
+ Socio-economic score	Least deprived	0.93	1.03	0.96	0.94	0.402	-	0.361	-
+ Overcrowding	Least overcrowded	1.05	0.98	0.93	0.98	0.418	-	0.267	-
+ Population density	Highest density	0.96	0.95	0.97	0.95	0.862	-	0.410	-
Socio-economic score	Least deprived	0.93	1.02	0.95	0.93	0.339	-	0.234	-
+ Region						0.312	-		
+ Population density	Highest density	0.94	0.91	0.94	0.91	0.494	-	0.158	-
Overcrowding	Least overcrowded	1.05	0.98	0.93	0.97	0.380	-	0.210	-
+ Region						0.295	-		
+ Population density	Highest density	0.95	0.92	0.95	0.93	0.647	-	0.242	-
Population density	Highest density	0.96	0.95	0.98	0.97	0.848	-	0.525	-
+ Region						0.280	-		
+ Socio-economic score	Least deprived	0.92	1.02	0.93	0.89	0.162	-	0.085	-
+ Overcrowding	Least overcrowded	1.04	0.97	0.91	0.94	0.257	-	0.072	-

Hodgkin lymphoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.183	-		
+ Socio-economic score	Least deprived	0.93	1.03	0.97	0.97	0.906	-	0.903	-
+ Overcrowding	Least overcrowded	1.02	0.88	0.95	0.98	0.620	-	0.801	-
+ Population density	Highest density	0.93	0.90	1.01	0.92	0.608	-	0.550	-
Socio-economic score	Least deprived	0.93	1.02	0.99	1.00	0.909	-	0.738	-
+ Region						0.182	-		
+ Population density	Highest density	0.93	0.89	1.00	0.90	0.614	-	0.515	-
Overcrowding	Least overcrowded	1.02	0.88	0.97	1.01	0.538	-	0.840	-
+ Region						0.210	-		
+ Population density	Highest density	0.94	0.90	1.02	0.91	0.681	-	0.622	-
Population density	Highest density	0.93	0.90	1.01	0.90	0.605	-	0.455	-
+ Region						0.184	-		
+ Socio-economic score	Least deprived	0.92	1.02	0.97	0.98	0.916	-	0.972	-
+ Overcrowding	Least overcrowded	1.01	0.87	0.96	0.98	0.610	-	0.819	-

Non-Hodgkin lymphoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.329	-		
+ Socio-economic score	Least deprived	0.91	1.00	0.91	0.88	0.358	-	0.112	-
+ Overcrowding	Least overcrowded	1.03	0.99	0.92	0.92	0.550	-	0.122	-
+ Population density	Highest density	0.99	1.00	0.97	1.00	0.996	-	0.854	-
Socio-economic score	Least deprived	0.91	1.00	0.90	0.85	0.182	-	0.040	*
+ Region						0.506	-		
+ Population density	Highest density	0.95	0.94	0.91	0.95	0.869	-	0.374	-
Overcrowding	Least overcrowded	1.03	0.98	0.91	0.90	0.323	-	0.047	*
+ Region						0.481	-		
+ Population density	Highest density	0.95	0.95	0.92	0.96	0.914	-	0.465	-
Population density	Highest density	0.99	1.01	0.99	1.04	0.994	-	0.825	-
+ Region						0.333	-		
+ Socio-economic score	Least deprived	0.91	0.99	0.88	0.82	0.122	-	0.025	*
+ Overcrowding	Least overcrowded	1.03	0.98	0.90	0.87	0.248	-	0.032	*

Table 3.10(c)

CNS and miscellaneous intra-cranial and intra-spinal neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.005	**		
+ Socio-economic score	Least deprived	0.95	0.92	0.91	0.88	0.017	*	<0.001	***
+ Overcrowding	Least overcrowded	1.00	0.91	0.92	0.90	0.007	**	<0.001	***
+ Population density	Highest density	1.12	1.09	1.07	1.15	0.004	**	0.011	*
Socio-economic score	Least deprived	0.95	0.93	0.92	0.89	0.045	*	0.002	**
+ Region						0.002	**		
+ Population density	Highest density	1.11	1.05	1.03	1.11	0.022	*	0.207	-
Overcrowding	Least overcrowded	1.00	0.91	0.92	0.90	0.007	**	<0.001	***
+ Region						0.005	**		
+ Population density	Highest density	1.11	1.06	1.04	1.12	0.021	*	0.178	-
Population density	Highest density	1.12	1.08	1.06	1.15	0.003	**	0.015	*
+ Region						0.007	**		
+ Socio-economic score	Least deprived	0.96	0.93	0.93	0.92	0.281	-	0.040	*
+ Overcrowding	Least overcrowded	1.01	0.91	0.93	0.93	0.051	-	0.021	*

Astrocytoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						<0.001	***		
+ Socio-economic score	Least deprived	0.93	0.82	0.86	0.83	0.018	*	0.003	**
+ Overcrowding	Least overcrowded	0.99	0.84	0.92	0.86	0.020	*	0.008	**
+ Population density	Highest density	1.13	1.07	1.16	1.17	0.093	-	0.034	*
Socio-economic score	Least deprived	0.96	0.85	0.91	0.89	0.173	-	0.065	-
+ Region						<0.001	***		
+ Population density	Highest density	1.15	1.07	1.14	1.19	0.064	-	0.062	-
Overcrowding	Least overcrowded	1.00	0.85	0.94	0.88	0.043	*	0.027	*
+ Region						<0.001	***		
+ Population density	Highest density	1.14	1.06	1.13	1.18	0.095	-	0.088	-
Population density	Highest density	1.15	1.08	1.15	1.20	0.032	*	0.020	*
+ Region						<0.001	***		
+ Socio-economic score	Least deprived	0.96	0.86	0.93	0.94	0.321	-	0.435	-
+ Overcrowding	Least overcrowded	1.00	0.85	0.95	0.93	0.126	-	0.221	-

Primitive neuroectodermal tumours (PNET)

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.842	-		
+ Socio-economic score	Least deprived	0.83	0.82	0.85	0.77	0.059	-	0.011	*
+ Overcrowding	Least overcrowded	0.93	0.93	0.88	0.83	0.245	-	0.023	*
+ Population density	Highest density	1.08	1.20	1.13	1.02	0.193	-	0.177	-
Socio-economic score	Least deprived	0.84	0.84	0.86	0.79	0.083	-	0.016	*
+ Region						0.757	-		
+ Population density	Highest density	1.06	1.15	1.07	0.98	0.430	-	0.497	-
Overcrowding	Least overcrowded	0.93	0.93	0.89	0.83	0.222	-	0.020	*
+ Region						0.866	-		
+ Population density	Highest density	1.06	1.15	1.08	0.97	0.438	-	0.545	-
Population density	Highest density	1.09	1.20	1.14	1.03	0.148	-	0.116	-
+ Region						0.901	-		
+ Socio-economic score	Least deprived	0.86	0.85	0.88	0.82	0.257	-	0.078	-
+ Overcrowding	Least overcrowded	0.94	0.94	0.90	0.86	0.607	-	0.111	-

Table 3.10(d)

Sympathetic nervous system tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.164	-		
+ Socio-economic score	Least deprived	1.13	1.19	1.12	1.13	0.354	-	0.244	-
+ Overcrowding	Least overcrowded	1.18	1.17	1.09	1.11	0.289	-	0.699	-
+ Population density	Highest density	1.01	0.97	1.08	0.93	0.660	-	0.944	-
Socio-economic score	Least deprived	1.12	1.17	1.10	1.10	0.456	-	0.439	-
+ Region						0.131	-		
+ Population density	Highest density	1.01	0.99	1.12	0.96	0.533	-	0.652	-
Overcrowding	Least overcrowded	1.18	1.17	1.08	1.09	0.290	-	0.913	-
+ Region						0.164	-		
+ Population density	Highest density	1.00	0.97	1.09	0.94	0.630	-	0.918	-
Population density	Highest density	1.00	0.97	1.10	0.94	0.596	-	0.808	-
+ Region						0.182	-		
+ Socio-economic score	Least deprived	1.12	1.18	1.12	1.12	0.403	-	0.286	-
+ Overcrowding	Least overcrowded	1.18	1.17	1.08	1.10	0.310	-	0.792	-

Table 3.10(e)

Retinoblastoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.035	*		
+ Socio-economic score	Least deprived	0.91	1.05	1.14	1.03	0.461	-	0.352	-
+ Overcrowding	Least overcrowded	1.06	0.95	1.11	0.98	0.635	-	0.915	-
+ Population density	Highest density	1.16	0.90	0.89	0.77	0.023	*	0.039	*
Socio-economic score	Least deprived	0.93	1.07	1.18	1.08	0.354	-	0.182	-
+ Region						0.046	*		
+ Population density	Highest density	1.19	0.95	0.98	0.89	0.093	-	0.334	-
Overcrowding	Least overcrowded	1.07	0.96	1.12	0.99	0.592	-	0.945	-
+ Region						0.038	*		
+ Population density	Highest density	1.16	0.90	0.91	0.82	0.047	*	0.080	-
Population density	Highest density	1.18	0.93	0.94	0.85	0.053	-	0.150	-
+ Region						0.017	*		
+ Socio-economic score	Least deprived	0.94	1.06	1.14	1.05	0.556	-	0.366	-
+ Overcrowding	Least overcrowded	1.07	0.95	1.09	0.94	0.539	-	0.593	-

Retinoblastoma – unilateral

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.002	**		
+ Socio-economic score	Least deprived	0.83	0.99	1.02	1.02	0.696	-	0.451	-
+ Overcrowding	Least overcrowded	0.99	0.82	0.99	0.86	0.509	-	0.310	-
+ Population density	Highest density	1.09	0.97	0.85	0.81	0.403	-	0.164	-
Socio-economic score	Least deprived	0.85	1.01	1.04	1.04	0.698	-	0.391	-
+ Region						0.002	**		
+ Population density	Highest density	1.12	1.00	0.92	0.95	0.708	-	0.559	-
Overcrowding	Least overcrowded	0.99	0.82	0.98	0.85	0.478	-	0.268	-
+ Region						0.002	**		
+ Population density	Highest density	1.05	0.91	0.81	0.82	0.416	-	0.111	-
Population density	Highest density	1.11	0.98	0.88	0.90	0.591	-	0.336	-
+ Region						<0.001	***		
+ Socio-economic score	Least deprived	0.85	1.00	1.02	1.01	0.817	-	0.594	-
+ Overcrowding	Least overcrowded	0.99	0.82	0.95	0.80	0.328	-	0.120	-

Retinoblastoma – bilateral

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.113	-		
+ Socio-economic score	Least deprived	1.07	1.13	1.31	1.04	0.565	-	0.714	-
+ Overcrowding	Least overcrowded	1.20	1.23	1.32	1.23	0.768	-	0.363	-
+ Population density	Highest density	1.20	0.74	0.96	0.71	0.051	-	0.119	-
Socio-economic score	Least deprived	1.09	1.16	1.37	1.10	0.493	-	0.498	-
+ Region						0.129	-		
+ Population density	Highest density	1.22	0.78	1.06	0.80	0.097	-	0.330	-
Overcrowding	Least overcrowded	1.22	1.25	1.36	1.24	0.692	-	0.325	-
+ Region						0.128	-		
+ Population density	Highest density	1.24	0.80	1.07	0.81	0.099	-	0.363	-
Population density	Highest density	1.24	0.78	1.05	0.80	0.084	-	0.285	-
+ Region						0.077	-		
+ Socio-economic score	Least deprived	1.09	1.13	1.32	1.04	0.551	-	0.743	-
+ Overcrowding	Least overcrowded	1.21	1.24	1.32	1.19	0.766	-	0.479	-

Table 3.10(f)

Renal tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.157	-		
+ Socio-economic score	Least deprived	0.93	0.87	0.99	0.90	0.304	-	0.411	-
+ Overcrowding	Least overcrowded	1.04	1.02	0.99	1.00	0.971	-	0.726	-
+ Population density	Highest density	1.07	1.03	1.12	1.07	0.665	-	0.278	-
Socio-economic score	Least deprived	0.93	0.87	0.98	0.86	0.159	-	0.110	-
+ Region						0.257	-		
+ Population density	Highest density	1.05	1.01	1.11	1.08	0.753	-	0.360	-
Overcrowding	Least overcrowded	1.04	1.02	0.96	0.96	0.767	-	0.283	-
+ Region						0.227	-		
+ Population density	Highest density	1.06	1.03	1.12	1.08	0.696	-	0.285	-
Population density	Highest density	1.07	1.04	1.14	1.10	0.513	-	0.142	-
+ Region						0.203	-		
+ Socio-economic score	Least deprived	0.93	0.88	1.00	0.89	0.265	-	0.321	-
+ Overcrowding	Least overcrowded	1.04	1.03	0.98	0.99	0.942	-	0.645	-

Table 3.10(g)

Hepatic tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.002	**		
+ Socio-economic score	Least deprived	0.87	0.86	1.11	1.09	0.664	-	0.345	-
+ Overcrowding	Least overcrowded	0.80	0.86	0.90	1.14	0.392	-	0.211	-
+ Population density	Highest density	1.06	0.99	0.79	1.07	0.828	-	0.656	-
Socio-economic score	Least deprived	0.84	0.81	1.04	1.02	0.701	-	0.485	-
+ Region						0.002	**		
+ Population density	Highest density	1.03	0.90	0.70	0.91	0.626	-	0.271	-
Overcrowding	Least overcrowded	0.78	0.85	0.88	1.17	0.233	-	0.138	-
+ Region						0.004	**		
+ Population density	Highest density	1.09	1.00	0.78	1.00	0.774	-	0.566	-
Population density	Highest density	1.02	0.90	0.68	0.86	0.502	-	0.157	-
+ Region						0.005	**		
+ Socio-economic score	Least deprived	0.83	0.79	0.97	0.93	0.836	-	0.963	-
+ Overcrowding	Least overcrowded	0.79	0.85	0.86	1.13	0.402	-	0.317	-

Hepatoblastoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.006	**		
+ Socio-economic score	Least deprived	1.10	0.98	1.24	1.12	0.880	-	0.547	-
+ Overcrowding	Least overcrowded	0.80	0.80	0.89	1.02	0.753	-	0.567	-
+ Population density	Highest density	1.10	1.02	0.90	1.20	0.928	-	0.940	-
Socio-economic score	Least deprived	1.08	0.95	1.19	1.12	0.899	-	0.535	-
+ Region						0.006	**		
+ Population density	Highest density	1.10	0.96	0.80	1.02	0.855	-	0.623	-
Overcrowding	Least overcrowded	0.79	0.79	0.88	1.07	0.581	-	0.394	-
+ Region						0.009	**		
+ Population density	Highest density	1.14	1.03	0.87	1.10	0.876	-	0.862	-
Population density	Highest density	1.08	0.94	0.77	0.98	0.801	-	0.462	-
+ Region						0.008	**		
+ Socio-economic score	Least deprived	1.07	0.93	1.15	1.06	0.943	-	0.751	-
+ Overcrowding	Least overcrowded	0.80	0.79	0.88	1.06	0.656	-	0.531	-

Hepatic carcinoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.076	-		
+ Socio-economic score	Least deprived	0.31	0.57	0.81	1.04	0.194	-	0.381	-
+ Overcrowding	Least overcrowded	0.76	1.13	0.94	1.67	0.381	-	0.109	-
+ Population density	Highest density	0.94	0.89	0.47	0.68	0.747	-	0.268	-
Socio-economic score	Least deprived	0.28	0.50	0.68	0.81	0.216	-	0.748	-
+ Region						0.069	-		
+ Population density	Highest density	0.83	0.72	0.39	0.55	0.608	-	0.140	-
Overcrowding	Least overcrowded	0.74	1.10	0.88	1.62	0.354	-	0.114	-
+ Region						0.081	-		
+ Population density	Highest density	0.94	0.90	0.51	0.67	0.843	-	0.354	-
Population density	Highest density	0.84	0.75	0.40	0.53	0.516	-	0.097	-
+ Region						0.115	-		
+ Socio-economic score	Least deprived	0.28	0.46	0.56	0.60	0.264	-	0.616	-
+ Overcrowding	Least overcrowded	0.74	1.08	0.82	1.39	0.634	-	0.334	-

Table 3.10(h)

Malignant bone tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.481	-		
+ Socio-economic score	Least deprived	0.95	1.13	0.90	0.89	0.043	*	0.108	-
+ Overcrowding	Least overcrowded	1.08	1.02	1.00	0.91	0.321	-	0.099	-
+ Population density	Highest density	1.09	1.09	1.13	1.10	0.627	-	0.203	-
Socio-economic score	Least deprived	0.95	1.13	0.89	0.87	0.015	*	0.033	*
+ Region						0.748	-		
+ Population density	Highest density	1.05	1.04	1.07	1.03	0.951	-	0.606	-
Overcrowding	Least overcrowded	1.09	1.01	0.98	0.89	0.139	-	0.032	*
+ Region						0.728	-		
+ Population density	Highest density	1.05	1.04	1.08	1.05	0.940	-	0.541	-
Population density	Highest density	1.09	1.09	1.15	1.13	0.489	-	0.100	-
+ Region						0.569	-		
+ Socio-economic score	Least deprived	0.95	1.13	0.91	0.89	0.048	*	0.138	-
+ Overcrowding	Least overcrowded	1.09	1.02	0.99	0.91	0.367	-	0.128	-

Osteosarcoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.985	-		
+ Socio-economic score	Least deprived	0.89	1.05	0.96	0.92	0.717	-	0.597	-
+ Overcrowding	Least overcrowded	0.93	0.98	0.91	0.91	0.916	-	0.423	-
+ Population density	Highest density	1.05	0.96	1.11	1.09	0.798	-	0.589	-
Socio-economic score	Least deprived	0.89	1.04	0.96	0.91	0.687	-	0.523	-
+ Region						0.989	-		
+ Population density	Highest density	1.03	0.94	1.09	1.08	0.813	-	0.724	-
Overcrowding	Least overcrowded	0.93	0.97	0.91	0.90	0.886	-	0.361	-
+ Region						0.990	-		
+ Population density	Highest density	1.03	0.93	1.08	1.06	0.820	-	0.774	-
Population density	Highest density	1.05	0.96	1.12	1.10	0.770	-	0.513	-
+ Region						0.989	-		
+ Socio-economic score	Least deprived	0.89	1.04	0.97	0.92	0.731	-	0.706	-
+ Overcrowding	Least overcrowded	0.93	0.97	0.91	0.91	0.929	-	0.459	-

Ewing's sarcoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.170	-		
+ Socio-economic score	Least deprived	1.01	1.16	0.78	0.81	0.022	*	0.026	*
+ Overcrowding	Least overcrowded	1.32	1.02	0.98	0.87	0.036	*	0.031	*
+ Population density	Highest density	1.19	1.36	1.18	1.21	0.159	-	0.094	-
Socio-economic score	Least deprived	1.00	1.14	0.76	0.77	0.005	**	0.004	**
+ Region						0.414	-		
+ Population density	Highest density	1.10	1.22	1.06	1.05	0.611	-	0.568	-
Overcrowding	Least overcrowded	1.32	1.01	0.95	0.83	0.010	**	0.007	**
+ Region						0.389	-		
+ Population density	Highest density	1.11	1.23	1.09	1.11	0.600	-	0.412	-
Population density	Highest density	1.17	1.34	1.23	1.25	0.152	-	0.043	*
+ Region						0.175	-		
+ Socio-economic score	Least deprived	1.02	1.16	0.78	0.81	0.029	*	0.038	*
+ Overcrowding	Least overcrowded	1.34	1.03	0.98	0.89	0.051	-	0.064	-

Table 3.10(i)

Soft-tissue sarcomas

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.183	-		
+ Socio-economic score	Least deprived	1.01	1.13	1.01	0.95	0.177	-	0.342	-
+ Overcrowding	Least overcrowded	1.14	0.95	1.05	0.95	0.070	-	0.160	-
+ Population density	Highest density	1.10	1.20	1.09	1.11	0.089	-	0.074	-
Socio-economic score	Least deprived	1.02	1.14	1.01	0.94	0.088	-	0.180	-
+ Region						0.298	-		
+ Population density	Highest density	1.08	1.18	1.09	1.11	0.187	-	0.105	-
Overcrowding	Least overcrowded	1.14	0.95	1.04	0.93	0.033	*	0.065	-
+ Region						0.304	-		
+ Population density	Highest density	1.08	1.18	1.08	1.12	0.202	-	0.116	-
Population density	Highest density	1.09	1.20	1.11	1.15	0.058	-	0.021	*
+ Region						0.248	-		
+ Socio-economic score	Least deprived	1.03	1.15	1.04	0.99	0.277	-	0.822	-
+ Overcrowding	Least overcrowded	1.15	0.96	1.07	0.99	0.119	-	0.447	-

Table 3.10(j)

Germ cell, trophoblastic and other gonadal neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.195	-		
+ Socio-economic score	Least deprived	1.01	0.78	0.91	1.00	0.139	-	0.975	-
+ Overcrowding	Least overcrowded	0.89	0.81	0.87	0.87	0.515	-	0.318	-
+ Population density	Highest density	1.02	1.02	0.97	0.89	0.927	-	0.590	-
Socio-economic score	Least deprived	1.04	0.81	0.94	1.03	0.169	-	0.720	-
+ Region						0.168	-		
+ Population density	Highest density	1.08	1.10	1.06	1.01	0.873	-	0.665	-
Overcrowding	Least overcrowded	0.90	0.81	0.88	0.87	0.527	-	0.278	-
+ Region						0.191	-		
+ Population density	Highest density	1.03	1.03	0.99	0.93	0.963	-	0.766	-
Population density	Highest density	1.05	1.05	1.02	0.96	0.951	-	0.989	-
+ Region						0.185	-		
+ Socio-economic score	Least deprived	1.05	0.81	0.95	1.07	0.138	-	0.634	-
+ Overcrowding	Least overcrowded	0.90	0.81	0.88	0.87	0.544	-	0.276	-

Table 3.10(k)

Carcinoma and other malignant epithelial neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.053	-		
+ Socio-economic score	Least deprived	0.91	0.96	0.83	0.77	0.126	-	0.013	*
+ Overcrowding	Least overcrowded	0.99	0.81	0.91	0.79	0.126	-	0.026	*
+ Population density	Highest density	0.91	0.97	1.00	1.16	0.602	-	0.523	-
Socio-economic score	Least deprived	0.94	0.99	0.85	0.80	0.130	-	0.015	*
+ Region						0.052	-		
+ Population density	Highest density	0.88	0.91	0.92	1.09	0.483	-	0.961	-
Overcrowding	Least overcrowded	1.00	0.82	0.90	0.78	0.066	-	0.010	*
+ Region						0.089	-		
+ Population density	Highest density	0.87	0.90	0.93	1.11	0.412	-	0.856	-
Population density	Highest density	0.93	0.99	1.04	1.25	0.386	-	0.213	-
+ Region						0.084	-		
+ Socio-economic score	Least deprived	0.93	0.98	0.85	0.78	0.169	-	0.025	*
+ Overcrowding	Least overcrowded	0.99	0.81	0.89	0.75	0.072	-	0.013	*

Table 3.10(l)

Other and unspecified malignant neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.002	**		
+ Socio-economic score	Least deprived	1.13	0.50	0.85	0.87	0.194	-	0.500	-
+ Overcrowding	Least overcrowded	0.74	0.75	0.71	0.81	0.828	-	0.570	-
+ Population density	Highest density	0.83	0.79	0.77	0.68	0.817	-	0.243	-
Socio-economic score	Least deprived	1.19	0.55	0.88	0.82	0.237	-	0.325	-
+ Region						0.001	**		
+ Population density	Highest density	0.83	0.83	0.81	0.79	0.932	-	0.466	-
Overcrowding	Least overcrowded	0.76	0.78	0.69	0.71	0.775	-	0.262	-
+ Region						0.002	**		
+ Population density	Highest density	0.80	0.79	0.81	0.78	0.895	-	0.452	-
Population density	Highest density	0.87	0.90	0.94	0.92	0.983	-	0.782	-
+ Region						0.001	**		
+ Socio-economic score	Least deprived	1.18	0.54	0.83	0.74	0.200	-	0.196	-
+ Overcrowding	Least overcrowded	0.75	0.77	0.66	0.63	0.647	-	0.149	-

Table 3.10(m)

All cancer

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						<0.001	***		
+ Socio-economic score	Least deprived	0.99	0.98	0.95	0.93	<0.001	***	<0.001	***
+ Overcrowding	Least overcrowded	1.03	0.96	0.96	0.94	<0.001	***	<0.001	***
+ Population density	Highest density	1.04	1.03	1.03	1.05	0.049	*	0.044	*
Socio-economic score	Least deprived	0.99	0.99	0.95	0.92	<0.001	***	<0.001	***
+ Region						0.003	**		
+ Population density	Highest density	1.02	1.00	1.00	1.01	0.473	-	0.954	-
Overcrowding	Least overcrowded	1.03	0.96	0.95	0.93	<0.001	***	<0.001	***
+ Region						0.002	**		
+ Population density	Highest density	1.03	1.00	1.01	1.02	0.418	-	0.740	-
Population density	Highest density	1.04	1.03	1.04	1.06	0.016	*	0.006	**
+ Region						<0.001	***		
+ Socio-economic score	Least deprived	0.99	0.99	0.95	0.92	<0.001	***	<0.001	***
+ Overcrowding	Least overcrowded	1.03	0.96	0.95	0.93	<0.001	***	<0.001	***

Table 3.10(n)

All cancer minus leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Region						0.007	**		
+ Socio-economic score	Least deprived	0.97	0.99	0.96	0.93	0.011	*	0.001	**
+ Overcrowding	Least overcrowded	1.04	0.95	0.96	0.94	<0.001	***	<0.001	***
+ Population density	Highest density	1.06	1.04	1.04	1.05	0.033	*	0.067	-
Socio-economic score	Least deprived	0.97	0.99	0.96	0.93	0.002	**	<0.001	***
+ Region						0.022	*		
+ Population density	Highest density	1.05	1.02	1.03	1.04	0.172	-	0.326	-
Overcrowding	Least overcrowded	1.04	0.95	0.96	0.93	<0.001	***	<0.001	***
+ Region						0.057	-		
+ Population density	Highest density	1.05	1.02	1.03	1.04	0.176	-	0.401	-
Population density	Highest density	1.06	1.04	1.06	1.07	0.009	**	0.008	**
+ Region						0.020	*		
+ Socio-economic score	Least deprived	0.97	0.99	0.97	0.94	0.056	-	0.010	*
+ Overcrowding	Least overcrowded	1.04	0.95	0.96	0.94	<0.001	***	<0.001	***

Table 3.11 Scotland, Census Wards. Regression analyses of crude incidence rates at ages 0–14 years for groups of wards categorised according to values of specified factors

The following table shows, for each diagnostic group, the relative risks at each level of three socio-demographic factors and also the values having allowed separately for each of the other factors. (There are no joint analyses for socio-economic score and overcrowding because these two variables are closely correlated.) The possible effect of each factor, and whether there is a trend in the effect related to the level of the factor, is indicated by the significance tests shown in the last two columns. The tests for each variable, without allowing for any of the others, are the same as those in Table 3.6.

* p<0.05 ** p<0.01 *** p<0.001 - non-significant

Table 3.11(a)

Leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.10	0.89	0.86	0.79	0.008	**	<0.001	***
+ Population density	Highest density	0.96	0.97	1.19	1.10	0.290	-	0.210	-
Overcrowding	Least overcrowded	1.22	1.01	0.92	0.84	0.002	**	<0.001	***
+ Population density	Highest density	0.97	0.97	1.17	1.10	0.429	-	0.248	-
Population density	Highest density	0.99	1.04	1.32	1.25	0.031	*	0.007	**
+ Socio-economic score	Least deprived	1.06	0.88	0.87	0.81	0.090	-	0.011	*
+ Overcrowding	Least overcrowded	1.16	0.99	0.92	0.85	0.037	*	0.009	**

Lymphoid and unspecified leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.07	0.86	0.84	0.74	0.004	**	<0.001	***
+ Population density	Highest density	1.00	1.05	1.17	1.12	0.707	-	0.212	-
Overcrowding	Least overcrowded	1.27	0.98	0.92	0.82	<0.001	***	<0.001	***
+ Population density	Highest density	1.02	1.07	1.15	1.13	0.801	-	0.227	-
Population density	Highest density	1.04	1.14	1.32	1.30	0.080	-	0.005	**
+ Socio-economic score	Least deprived	1.04	0.85	0.85	0.77	0.061	-	0.006	**
+ Overcrowding	Least overcrowded	1.23	0.96	0.92	0.84	0.015	*	0.008	**

Table 3.11(b)

Lymphomas and reticuloendothelial neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.74	0.62	0.71	0.67	0.086	-	0.029	*
+ Population density	Highest density	1.30	0.82	1.22	1.48	0.032	*	0.407	-
Overcrowding	Least overcrowded	1.05	0.93	1.03	0.68	0.027	*	0.017	*
+ Population density	Highest density	1.22	0.72	1.02	1.24	0.033	*	0.847	-
Population density	Highest density	1.32	0.85	1.26	1.51	0.034	*	0.280	-
+ Socio-economic score	Least deprived	0.70	0.62	0.68	0.68	0.080	-	0.033	*
+ Overcrowding	Least overcrowded	1.04	0.94	1.01	0.65	0.025	*	0.018	*

Hodgkin lymphoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.57	0.58	0.82	0.66	0.223	-	0.337	-
+ Population density	Highest density	1.59	1.00	1.33	2.04	0.087	-	0.235	-
Overcrowding	Least overcrowded	1.07	1.03	1.15	0.72	0.272	-	0.189	-
+ Population density	Highest density	1.49	0.84	1.03	1.52	0.115	-	0.845	-
Population density	Highest density	1.60	0.99	1.25	1.81	0.094	-	0.321	-
+ Socio-economic score	Least deprived	0.52	0.57	0.79	0.71	0.208	-	0.444	-
+ Overcrowding	Least overcrowded	1.10	1.05	1.14	0.72	0.326	-	0.238	-

Non-Hodgkin lymphoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.74	0.64	0.58	0.68	0.242	-	0.081	-
+ Population density	Highest density	1.24	0.69	1.14	1.20	0.190	-	0.989	-
Overcrowding	Least overcrowded	0.85	0.81	0.89	0.62	0.300	-	0.076	-
+ Population density	Highest density	1.15	0.62	1.02	1.05	0.165	-	0.586	-
Population density	Highest density	1.25	0.73	1.21	1.27	0.245	-	0.820	-
+ Socio-economic score	Least deprived	0.72	0.64	0.55	0.66	0.188	-	0.051	-
+ Overcrowding	Least overcrowded	0.83	0.81	0.87	0.57	0.204	-	0.050	-

Table 3.11(c)

CNS and miscellaneous intra-cranial and intra-spinal neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.03	1.07	0.95	0.80	0.069	-	0.019	*
+ Population density	Highest density	1.01	1.06	1.05	1.13	0.963	-	0.479	-
Overcrowding	Least overcrowded	1.20	1.01	1.03	0.85	0.040	*	0.022	*
+ Population density	Highest density	1.04	1.09	1.04	1.14	0.935	-	0.454	-
Population density	Highest density	1.06	1.16	1.18	1.27	0.402	-	0.049	*
+ Socio-economic score	Least deprived	1.01	1.06	0.95	0.82	0.262	-	0.091	-
+ Overcrowding	Least overcrowded	1.20	1.01	1.04	0.88	0.144	-	0.088	-

Astrocytoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.28	1.06	1.00	0.93	0.528	-	0.290	-
+ Population density	Highest density	0.99	0.90	0.97	1.28	0.794	-	0.754	-
Overcrowding	Least overcrowded	1.12	0.88	0.88	0.80	0.367	-	0.071	-
+ Population density	Highest density	1.00	0.90	0.97	1.30	0.761	-	0.749	-
Population density	Highest density	1.02	0.97	1.08	1.48	0.607	-	0.299	-
+ Socio-economic score	Least deprived	1.23	1.06	0.99	0.92	0.709	-	0.405	-
+ Overcrowding	Least overcrowded	1.10	0.88	0.89	0.79	0.486	-	0.110	-

Primitive neuroectodermal tumours (PNET)

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.83	1.13	0.95	0.80	0.582	-	0.380	-
+ Population density	Highest density	0.94	1.11	1.15	0.82	0.855	-	0.777	-
Overcrowding	Least overcrowded	1.25	0.71	1.04	0.97	0.353	-	0.660	-
+ Population density	Highest density	1.00	1.25	1.23	0.86	0.723	-	0.552	-
Population density	Highest density	0.99	1.21	1.25	0.86	0.708	-	0.474	-
+ Socio-economic score	Least deprived	0.84	1.12	0.97	0.83	0.728	-	0.580	-
+ Overcrowding	Least overcrowded	1.23	0.70	1.03	1.02	0.363	-	0.879	-

Table 3.11(d)

Sympathetic nervous system tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.78	0.70	0.82	0.62	0.178	-	0.038	*
+ Population density	Highest density	0.87	1.05	0.81	0.87	0.789	-	0.628	-
Overcrowding	Least overcrowded	0.82	0.85	0.86	0.67	0.425	-	0.095	-
+ Population density	Highest density	0.88	1.06	0.84	0.88	0.839	-	0.678	-
Population density	Highest density	0.93	1.19	0.94	1.00	0.790	-	0.809	-
+ Socio-economic score	Least deprived	0.80	0.70	0.83	0.60	0.177	-	0.039	*
+ Overcrowding	Least overcrowded	0.85	0.86	0.87	0.67	0.464	-	0.110	-

Table 3.11(e)

Retinoblastoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.88	1.26	1.10	0.93	0.833	-	0.915	-
+ Population density	Highest density	1.18	0.59	1.20	0.38	0.089	-	0.354	-
Overcrowding	Least overcrowded	0.64	0.83	1.09	0.65	0.243	-	0.512	-
+ Population density	Highest density	1.13	0.55	1.20	0.37	0.069	-	0.292	-
Population density	Highest density	1.26	0.66	1.34	0.41	0.100	-	0.528	-
+ Socio-economic score	Least deprived	0.94	1.28	1.04	0.86	0.782	-	0.670	-
+ Overcrowding	Least overcrowded	0.60	0.81	0.99	0.56	0.171	-	0.288	-

Retinoblastoma – unilateral

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.59	1.19	1.47	1.23	0.473	-	0.260	-
+ Population density	Highest density	1.27	1.05	2.55	0.59	0.167	-	0.241	-
Overcrowding	Least overcrowded	0.85	1.30	1.63	1.20	0.631	-	0.427	-
+ Population density	Highest density	1.19	0.91	2.16	0.47	0.221	-	0.473	-
Population density	Highest density	1.22	0.89	1.96	0.40	0.233	-	0.604	-
+ Socio-economic score	Least deprived	0.55	1.13	1.51	1.45	0.352	-	0.135	-
+ Overcrowding	Least overcrowded	0.69	1.17	1.45	1.18	0.605	-	0.327	-

Retinoblastoma – bilateral

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.34	1.36	0.84	0.67	0.482	-	0.187	-
+ Population density	Highest density	1.15	0.31	0.46	0.26	0.044	*	0.017	*
Overcrowding	Least overcrowded	0.34	0.55	0.71	0.32	0.097	-	0.098	-
+ Population density	Highest density	1.13	0.33	0.62	0.35	0.106	-	0.057	-
Population density	Highest density	1.38	0.47	0.77	0.48	0.235	-	0.195	-
+ Socio-economic score	Least deprived	1.66	1.49	0.73	0.50	0.103	-	0.048	*
+ Overcrowding	Least overcrowded	0.37	0.58	0.66	0.25	0.042	*	0.024	*

Table 3.11(f)

Renal tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.08	0.72	1.23	1.25	0.251	-	0.177	-
+ Population density	Highest density	1.14	0.73	1.00	0.72	0.416	-	0.407	-
Overcrowding	Least overcrowded	0.88	0.71	0.95	1.11	0.458	-	0.329	-
+ Population density	Highest density	1.12	0.71	1.01	0.74	0.380	-	0.389	-
Population density	Highest density	1.10	0.66	0.91	0.67	0.223	-	0.148	-
+ Socio-economic score	Least deprived	1.12	0.73	1.17	1.17	0.462	-	0.446	-
+ Overcrowding	Least overcrowded	0.88	0.71	0.91	1.02	0.712	-	0.699	-

Table 3.11(g)

Hepatic tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.57	1.76	0.65	1.24	0.661	-	0.825	-
+ Population density	Highest density	0.82	0.56	1.18	0.70	0.877	-	0.846	-
Overcrowding	Least overcrowded	2.12	1.17	1.90	1.08	0.707	-	0.762	-
+ Population density	Highest density	0.75	0.54	1.03	0.70	0.883	-	0.722	-
Population density	Highest density	0.82	0.63	1.38	0.85	0.873	-	0.956	-
+ Socio-economic score	Least deprived	1.53	1.79	0.64	1.14	0.667	-	0.793	-
+ Overcrowding	Least overcrowded	1.92	1.12	1.81	0.93	0.719	-	0.727	-

Hepatoblastoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.76	1.59	0.65	1.63	0.724	-	0.839	-
+ Population density	Highest density	0.79	0.30	1.96	1.17	0.427	-	0.678	-
Overcrowding	Least overcrowded	0.85	1.17	1.09	1.08	0.997	-	0.850	-
+ Population density	Highest density	0.69	0.27	1.99	1.21	0.344	-	0.675	-
Population density	Highest density	0.70	0.27	1.77	1.09	0.389	-	0.754	-
+ Socio-economic score	Least deprived	1.46	1.56	0.65	1.62	0.775	-	0.794	-
+ Overcrowding	Least overcrowded	0.57	0.97	0.97	0.95	0.973	-	0.811	-

Hepatic carcinoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.18	2.12	0.65	0.47	0.763	-	0.447	-
+ Population density	Highest density	0.93	1.03	0.00	0.00	0.551	-	0.301	-
Overcrowding	Least overcrowded								
+ Population density	Highest density								
Population density	Highest density	1.22	1.88	0.00	0.00	0.641	-	0.665	-
+ Socio-economic score	Least deprived	1.67	2.27	0.63	0.39	0.667	-	0.377	-
+ Overcrowding	Least overcrowded								

Table 3.11(h)

Malignant bone tumours

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.56	1.16	1.12	0.98	0.284	-	0.527	-
+ Population density	Highest density	0.74	1.05	0.64	0.63	0.367	-	0.322	-
Overcrowding	Least overcrowded	2.00	1.28	1.33	1.70	0.225	-	0.429	-
+ Population density	Highest density	0.82	1.17	0.59	0.55	0.208	-	0.240	-
Population density	Highest density	0.77	1.08	0.63	0.56	0.290	-	0.226	-
+ Socio-economic score	Least deprived	0.60	1.18	1.14	0.92	0.359	-	0.764	-
+ Overcrowding	Least overcrowded	2.25	1.34	1.37	1.68	0.159	-	0.600	-

Osteosarcoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.52	1.29	1.74	1.09	0.124	-	0.299	-
+ Population density	Highest density	0.87	1.14	0.63	0.69	0.756	-	0.555	-
Overcrowding	Least overcrowded	1.87	2.03	1.31	2.01	0.430	-	0.347	-
+ Population density	Highest density	1.01	1.28	0.60	0.59	0.561	-	0.504	-
Population density	Highest density	0.94	1.16	0.60	0.59	0.647	-	0.404	-
+ Socio-economic score	Least deprived	0.57	1.31	1.76	1.05	0.156	-	0.388	-
+ Overcrowding	Least overcrowded	2.17	2.15	1.34	2.04	0.364	-	0.443	-

Ewing's sarcoma

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.43	0.96	0.65	0.85	0.505	-	0.951	-
+ Population density	Highest density	0.61	1.07	0.54	0.74	0.460	-	0.521	-
Overcrowding	Least overcrowded	1.70	0.52	1.18	1.26	0.267	-	0.874	-
+ Population density	Highest density	0.63	1.17	0.48	0.62	0.316	-	0.387	-
Population density	Highest density	0.61	1.10	0.52	0.63	0.375	-	0.394	-
+ Socio-economic score	Least deprived	0.46	0.98	0.68	0.80	0.608	-	0.741	-
+ Overcrowding	Least overcrowded	1.91	0.55	1.24	1.24	0.223	-	0.984	-

Table 3.11(i)

Soft-tissue sarcomas

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.82	0.93	0.91	0.86	0.950	-	0.654	-
+ Population density	Highest density	0.79	0.70	0.90	0.75	0.532	-	0.315	-
Overcrowding	Least overcrowded	1.12	1.00	0.91	0.86	0.798	-	0.270	-
+ Population density	Highest density	0.80	0.69	0.83	0.67	0.451	-	0.149	-
Population density	Highest density	0.83	0.76	0.97	0.79	0.657	-	0.418	-
+ Socio-economic score	Least deprived	0.83	0.95	0.90	0.78	0.838	-	0.379	-
+ Overcrowding	Least overcrowded	1.11	1.00	0.89	0.77	0.574	-	0.134	-

Table 3.11(j)

Germ cell, trophoblastic and other gonadal neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	1.09	1.47	0.70	1.26	0.254	-	0.783	-
+ Population density	Highest density	1.59	0.52	0.85	0.93	0.021	*	0.334	-
Overcrowding	Least overcrowded	1.31	0.85	0.84	1.14	0.648	-	0.988	-
+ Population density	Highest density	1.60	0.56	0.84	0.89	0.031	*	0.344	-
Population density	Highest density	1.54	0.55	0.90	0.98	0.037	*	0.335	-
+ Socio-economic score	Least deprived	1.16	1.51	0.63	1.12	0.155	-	0.802	-
+ Overcrowding	Least overcrowded	1.44	0.90	0.80	1.03	0.570	-	0.589	-

Table 3.11(k)

Carcinoma and other malignant epithelial neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.92	0.76	0.93	0.90	0.973	-	0.844	-
+ Population density	Highest density	0.98	0.82	1.25	0.76	0.861	-	0.970	-
Overcrowding	Least overcrowded	0.72	0.66	0.75	0.80	0.882	-	0.756	-
+ Population density	Highest density	0.98	0.82	1.35	0.79	0.797	-	0.933	-
Population density	Highest density	0.98	0.81	1.24	0.76	0.861	-	0.947	-
+ Socio-economic score	Least deprived	0.92	0.76	0.93	0.89	0.974	-	0.789	-
+ Overcrowding	Least overcrowded	0.65	0.63	0.72	0.77	0.820	-	0.685	-

Table 3.11(l)

Other and unspecified malignant neoplasms

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.00	1.06	1.31	1.17	0.436	-	0.430	-
+ Population density	Highest density	1.31	2.42	1.22	0.00	0.716	-	0.708	-
Overcrowding	Least overcrowded	0.85	0.39	0.54	1.08	0.813	-	0.813	-
+ Population density	Highest density	1.40	2.50	1.07	0.00	0.604	-	0.842	-
Population density	Highest density	1.22	1.88	0.77	0.00	0.679	-	0.878	-
+ Socio-economic score	Least deprived	0.00	1.02	1.41	1.44	0.466	-	0.365	-
+ Overcrowding	Least overcrowded	1.01	0.41	0.55	1.31	0.736	-	0.794	-

Table 3.11(m)

All cancer

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.96	0.91	0.89	0.82	0.003	**	<0.001	***
+ Population density	Highest density	1.01	0.92	1.07	1.02	0.225	-	0.803	-
Overcrowding	Least overcrowded	1.13	0.96	0.97	0.85	<0.001	***	<0.001	***
+ Population density	Highest density	1.02	0.92	1.04	0.99	0.318	-	0.775	-
Population density	Highest density	1.04	0.98	1.15	1.10	0.090	-	0.067	-
+ Socio-economic score	Least deprived	0.95	0.91	0.89	0.82	0.008	**	<0.001	***
+ Overcrowding	Least overcrowded	1.11	0.95	0.96	0.84	<0.001	***	<0.001	***

Table 3.11(n)

All cancer minus leukaemia

Factor	Relative risks for quintile group					Significance tests (p) for heterogeneity		Significance tests (p) for trend	
	1 (reference group)	2	3	4	5				
Socio-economic score	Least deprived	0.89	0.92	0.91	0.83	0.089	-	0.013	*
+ Population density	Highest density	1.04	0.90	1.01	0.97	0.325	-	0.558	-
Overcrowding	Least overcrowded	1.08	0.93	0.99	0.86	0.007	**	0.003	**
+ Population density	Highest density	1.04	0.89	0.97	0.93	0.238	-	0.242	-
Population density	Highest density	1.07	0.96	1.08	1.03	0.422	-	0.721	-
+ Socio-economic score	Least deprived	0.89	0.92	0.90	0.82	0.065	-	0.008	**
+ Overcrowding	Least overcrowded	1.09	0.93	0.98	0.83	0.003	**	0.002	**

Table 3.12 Annual registration rates per million children aged 0–4 years for England, Wales and Scotland county districts and England and Wales wards each categorised by socio-economic status

(a) Leukaemia

Quintile	England, Wales and Scotland county districts (1969–1993)	England and Wales wards (1969–1993)	England and Wales wards (1976–1985)
1 Least deprived	64.9	63.6	62.0
2	65.9	68.6	70.8
3	59.2	62.6	59.0
4	59.9	61.9	58.2
5 Most deprived	57.8	55.8	53.7

(b) CNS/brain

Quintile	England, Wales and Scotland county districts (1969–1993)	England and Wales wards (1969–1993)	England and Wales wards (1976–1985)
1 Least deprived	30.1	30.4	28.7
2	29.4	29.5	27.4
3	28.2	30.5	28.4
4	28.4	28.7	29.5
5 Most deprived	26.9	26.4	28.3

Table 3.13 Hodgkin lymphoma: age-specific rate (per million) for age 0–9 years for England, Wales and Scotland county districts and wards subdivided by quintiles of socio-economic status, degree of overcrowding, population density and urban/rural classification

Carstairs index of socio-economic status

Quintile	1969–1993 EWS county districts		1969–1993 England and Wales wards		1969–1993 Scotland wards		1976–1985 England and Wales wards	
	No	Rate	No	Rate	No	Rate	No	Rate
1 Least deprived	73	2.4	49	2.0	13	4.7	22	2.3
2	51	1.8	52	2.2	6	2.5	27	2.9
3	71	2.4	73	2.7	3	1.1	30	2.9
4	109	2.7	87	2.4	10	2.3	27	1.9
5 Most deprived	183	3.0	176	3.1	18	3.0	64	3.0

Degree of overcrowding

Quintile	1969–1993 EWS county districts		1969–1993 England and Wales wards		1969–1993 Scotland wards		1976–1985 England and Wales wards	
	No	Rate	No	Rate	No	Rate	No	Rate
1 Least overcrowded	46	1.8	52	2.3	9	4.0	22	2.5
2	60	2.1	58	2.3	6	2.3	29	2.9
3	71	2.1	50	1.8	8	2.8	20	1.8
4	155	3.1	91	2.6	13	3.1	33	2.5
5 Most overcrowded	155	3.0	186	3.2	14	2.2	66	3.1

Population density

Quintile	1969–1993 EWS county districts		1969–1993 England and Wales wards		1969–1993 Scotland wards		1976–1985 England and Wales wards	
	No	Rate	No	Rate	No	Rate	No	Rate
1 Highest density	167	2.6	172	3.0	16	2.5	63	3.0
2	137	2.9	111	2.3	16	3.0	45	2.5
3	83	2.6	82	2.3	11	3.2	34	2.5
4	64	2.3	53	2.7	5	2.4	20	2.6
5 Lowest density	36	2.2	19	1.9	2	2.4	8	2.1

Urban/rural classification

Quintile	1969–1993 EWS county districts		1969–1993 England and Wales wards		1969–1993 Scotland wards		1976–1985 England and Wales wards	
	No	Rate	No	Rate	No	Rate	No	Rate
1 Most urbanised	156	2.6	307	2.6	10	2.3	119	2.7
2	128	2.7	82	2.7	8	2.4	32	2.8
3	99	2.6	17	2.4	19	3.6	5	1.8
4	55	2.1	4	1.7	9	2.3	1	1.1
5 Most rural	49	2.6	5	5.0	4	3.3	4	10.4
6 Most rural (EW wards)			22	2.1			9	2.2

ANNEX 3A

ABSTRACT OF PAPER TO BE SUBMITTED FOR PUBLICATION
(UNPUBLISHED DATA USED WITH PERMISSION)

The data on which this paper is based overlap with those analysed in this report. Some of the analyses are similar but those relating to population mixing, a topic discussed in Chapter 2 and referred to in paragraph 3.30, are new.

Population Mixing, Socio-economic Status and Incidence of Childhood Acute Lymphoblastic Leukaemia in England and Wales – Analysis by Census Ward

CA Stiller and ME Kroll, Childhood Cancer Research Group, University of Oxford
PJ Boyle and Z Feng, School of Geography and Geosciences, University of St Andrews

There is increasing evidence from epidemiological studies that infection may be important in the aetiology of childhood acute lymphoblastic leukaemia (ALL). Kinlen's population-mixing hypothesis predicts an excess of childhood leukaemia in previously isolated places following a diverse population influx. Greaves predicts an excess of common ALL – the main subtype in early childhood – in children undergoing immune stress following unusually delayed exposure to infection.

We used Poisson regression to relate incidence of childhood ALL in small geographical areas to a range of relevant demographic variables. For each census ward in England and Wales, the number of cases of ALL diagnosed during 1986–1995 in children aged under 15 years was extracted from the population-based National Registry of Childhood Tumours; three categories of rurality (urban/mixed/rural), and quintile categories of affluence as categorised by the Carstairs index, population density, the proportion of incomers in the ward (people who had lived in a different ward a year before census day) and the diversity of their wards of origin, were derived from 1991 census data.

There was no evidence of association with any variable for ALL diagnosed at ages 0, 5–9 or 10–14 years. For ALL diagnosed at ages 1–4 years, there was only statistically significant univariate heterogeneity with diversity of incomers ($p=0.04$) and affluence ($p=0.011$), and a borderline significant association with rurality ($p=0.057$). The population-mixing model, combining diversity and rurality, was statistically significant ($p=0.008$); diversity and rurality each contributed independently and significantly. Incidence tended to be higher in rural wards with higher diversity of incomers ($p=0.042$ for trend), and in more affluent wards ($p=0.0014$ for trend). Adjusting for affluence reduced the association with population mixing ($p=0.087$), and *vice versa* ($p=0.154$).

The association with diversity of incomers, especially in rural areas, is consistent with the higher incidence of leukaemia predicted by Kinlen in areas where population mixing results in below average herd immunity to an infectious agent. The apparent specificity of the association to early childhood suggests that the effect may be specific to common ALL, as predicted by

Greaves. Affluence might be a confounder for this association, or might be related to ALL through similar underlying factors. This study provides further evidence that the risk of common ALL in children may be increased by delayed exposure to unknown common infections following relative geographical or social isolation early in life.

ANNEX 3B

METHODS

National Registry of Childhood Tumours

3B.1 The analyses in this chapter are based on information relating to cases included in the National Registry of Childhood Tumours (NRCT). The NRCT is a population-based registry, maintained by the Childhood Cancer Research Group in Oxford, covering the whole of England, Wales and Scotland (Stiller et al, 1995). It includes records for nearly all children under the age of 15 years diagnosed with malignant disease from 1962 onwards together with most children who died of cancer from 1953 onwards.

3B.2 The primary sources of data are the regional registries located throughout England, Wales and Scotland; these registries provide data directly to the NRCT as well as to the national cancer registries maintained (for England and Wales) by the Office for National Statistics (ONS – which includes the former OPCS) and (for Scotland) by the Information and Statistics Division (ISD). The ONS and the ISD also notify the NRCT of all deaths occurring before age 20 years with cancer coded as the underlying cause.

3B.3 In addition, there are a number of regional specialist childhood tumour registries that make their data available to the NRCT. The United Kingdom Children's Cancer Study Group (UKCCSG), which is the national organisation for paediatric oncologists, maintains a register of all children under the care of its members, and the NRCT is notified of these. The Clinical Trial Service Unit in Oxford notifies the NRCT of all children who have been entered into any of the leukaemia treatment trials sponsored previously by the Medical Research Council and now by the National Cancer Research Institute. Hence most children with cancer are notified to the NRCT from more than one source and it is believed that this has resulted in the ascertainment of virtually all leukaemia cases and in excess of 90% of other childhood cancers.

3B.4 Further information (such as histological review, and long-term follow-up) for many of the children in the registry is obtained from hospital records, general practitioner notes and the National Health Service Central Registers. As a result of this, the diagnostic data are of a much higher quality than those usually available from registry data for adults. Geographical information on residence at diagnosis and death, derived from address postcodes, is also added for all cases.

Classification of childhood cancers

3B.5 Malignancies in childhood can be categorised into 12 broad diagnostic groups based on the ICDO-2 classification of tumour site and histological type. This system, the International Classification of Childhood Cancer (ICCC), is used, for instance, in the IARC publication *International Incidence of Childhood Cancer* (Parkin et al, 1998). These 12 groups together with other diagnostic groups used in this chapter are listed in Table 1.1. Results are presented for each of these groups. The diagnostic subgroups have been included either in order to have more specific categories or because certain of these subgroups are thought to be more likely to show relationships with the socio-demographic variables.

Cases included in the present study

3B.6 The data relate to cases of childhood cancer, defined here as malignant tumours together with non-malignant tumours of the brain and central nervous system (CNS), occurring in the first 15 years of life, diagnosed, and normally resident, in Great Britain between 1969 and 1993, a 25-year period centred on the 1981 census, and for which there is a high level of completeness and diagnostic quality. Where a date of diagnosis is unknown the date of cancer registration is used, or a date of death if neither of the former is known; to be included, the child had to be under age 15 years at the date used.

Areas and population data

3B.7 Age-specific and age-standardised rates have been calculated at four geographical levels: county districts (of which there are 459), the Registrar General's Standard Regions for England (8), counties (67), and countries (3). Rates are also given for England and Wales taken together and for the whole of Great Britain. Standardised rates are calculated on the basis of a uniform age distribution. The smallest area unit for which data are available is the (1981) census ward or, equivalently, in Scotland the postcode sector. We shall refer to these as census wards or simply 'wards'. Rates have been calculated for aggregations of wards in England and Wales and in Scotland, these aggregations being defined according to socio-economic status, degree of overcrowding, population density and urban/rural classification. The average population in each of these types of area, together with an indication of the range of child population in each is given in Table 1.2.

3B.8 All diagnosis and death addresses received by the NRCT are postcoded. Using this postcode other geographical references can be attached to each case, the most useful of these being the grid reference and the 1981 census enumeration district that contains the majority of the unit postcode. This gives a fairly accurate location for the place of residence of the child. Using the enumeration district code each case can be assigned to a county (first two digits of the enumeration district code) to a county district (first four digits) and to a census ward (first six digits). Standard Regions are defined as aggregations of specified counties. Each grid reference is for a postcode rather than for a specific address, but this is sufficiently accurate for allocating cases to county, county district and ward. Although the case data cover a 25-year period, all postcodes have been allocated to enumeration districts as they existed at the 1981 census. This enables analyses to be carried out for the complete timespan of the data.

3B.9 For the calculation of rates at county district and higher level the populations used were those produced annually by the ONS for England and Wales and the General Register Office for Scotland (GROS). These populations are provided for county districts and are based on the decennial census figures annually adjusted for births, deaths, and migration, etc. Figures for the counties, the Standard Regions, and the country totals were derived by summation of these county district data.

3B.10 At the ward level, population data are only available from the decennial censuses: for this report these data have been obtained from the 1971, 1981 and 1991 censuses. Enumeration districts and wards cover different geographical areas at each successive census; hence, in order to analyse the ward rates over a long time period it was necessary to define areas that were, as far as possible, unchanged over the time period covered by this report. Much work has been done elsewhere (Dorling, 1991) in deriving look-up tables that enable 1971 and 1991 census enumeration districts (the smallest areas for which census data are available) to be amalgamated into areas that approximate to the 1981 census wards. In this way the population for each of these three years can be derived for areas that are based on the 1981 wards. Linear

interpolation was used to estimate populations for the intercensal years; the 1971 population was used as an estimate for 1969 and 1970, and the 1991 population was used as an estimate for 1992 and 1993.

Classifications of county districts

3B.11 In order to identify possible effects of socio-economic status, degree of overcrowding, population density and urban/rural classification on childhood cancer incidence rates, a score for each of these four variables was calculated for each county district as described in paragraphs 3B.12–3B.15. The county districts were then grouped using the scores for each of the variables in turn, and age-standardised rates tabulated for the totality of county districts falling into each of the resulting groups.

Socio-economic score

3B.12 The socio-economic score is based on the index of social deprivation proposed by Carstairs and Morris (1989). Variables relating to male employment, overcrowding, car ownership and social class were extracted for county districts from the 1981 census data held at the University of Manchester. For each variable a 'z-score' was formed by taking the difference between the individual county district value and the mean of all county district values and dividing this by the standard deviation of all the county district values. From these an overall score, based on the Carstairs formula, was calculated by adding together the 'z-scores' for each of these variables. The quintiles for this overall score were calculated, and county districts were grouped into five categories with boundaries defined by the quintiles.

Overcrowding

3B.13 The measure of overcrowding is calculated as the number of people living in households with one or more persons per room as a proportion of all residents in households. Hence lower values of this measure correspond to less overcrowding.

Population density

3B.14 The population density is based on the areas in hectares for county districts from the 1981 census data held at the University of Manchester, and the averaged 1971, 1981 and 1991 census populations for all ages; use of the all-ages population seems a more appropriate measure of population density than using simply the child population.

Urban/rural classification

3B.15 The classification of urban/rural status for 1981 census wards (postcode sectors in Scotland) is explained in paragraph 3B.17. For each county district we have derived a value based on the population weighted mean of the values given for all the wards/postcode sectors falling within this county district. The populations used for weighting the wards/postcode sectors were the averages of the 1971, 1981 and 1991 census populations for all children aged 0–14 years. As explained in paragraph 3B.17, the index for Scottish wards, and hence that for Scottish county districts, is not directly comparable to that for England and Wales, but we have assumed that the use of this index will result in Scottish county districts being allocated to approximately the correct quintile. For both England/Wales and Scotland the analyses by urban/rural status at county district level should, however, be treated with some caution since there are obvious problems in extrapolating from an enumeration district classification to a classification for a whole county district; even in 'rural' county districts the population is likely to be concentrated in the towns within that district.

Classifications of census wards

3B.16 We have carried out similar analyses of the same socio-demographic variables for census wards for the same period. The definitions of socio-economic score, overcrowding and population density are analogous to those described for county districts in paragraphs 3B.12–3B.14. That for the urban/rural index is explained in paragraph 3B.17.

Urban/rural classification

3B.17 The urban/rural indices at ward level (postcode sectors in Scotland) are derived from a classification of 1981 enumeration districts – *but the method of classification of enumeration districts for England and Wales is different from that used for Scotland.* In England and Wales, enumeration districts were each classified as 'urban' or 'rural' by the ONS and then wards were grouped, again by the ONS, into six categories according to the percentage of their enumeration districts that was 'urban'. In Scotland, however, enumeration districts were grouped into five categories according to the type of area in which they were situated. These were used at the CCRG to create a value for each ward/postcode sector by weighting the values for the enumeration districts within each such sector by the 1981 enumeration district population of children aged 0–14 years, and rounding the value of the resulting average to the nearest integer; this gives five categories corresponding to the original five enumeration district categories. In using these different scoring systems in England/Wales and in Scotland it is likely that some Scottish wards will be displaced to a higher or lower category than if the same system had been used as for England and Wales. However, since the categories given by either of these systems are essentially empirical, and even their relative ordering open to question, it was decided not to attempt to achieve any greater degree of comparability. These differences in definition have made it necessary to analyse England and Wales wards separately from those for Scotland. This does, however, have the advantage of providing two sets of results for each factor, and these results can be compared to see whether they are consistent.

Poisson regression analyses

3B.18 For wards, in addition to the tabular presentation of rates by groups of wards categorised according to values of the socio-demographic variables, we have used Poisson regression to give some quantitative estimate of the effects of the factors described in previous paragraphs, ie to estimate the amounts by which the incidence rates change between groups of wards having different values for the socio-demographic factors. The tabular and regression analyses for wards overlap to a great extent; the factors analysed differ in that only the tables include analyses of urban/rural status while only the regressions include analyses of Standard Region. The tabular presentation is more easily understood. The regression method of analysis has the advantage that it quantifies some of the effects seen in the tables, and makes it possible to examine and quantify the effects of two or more factors simultaneously, though at the expense of making a number of assumptions about the ways in which the factors are related to the incidence rates. (Specifically, we fitted a log linear model in which the number of cases in a ward (or county district) is a Poisson variable where the mean depends multiplicatively on the socio-demographic factor.) The effects of the factors, and of one factor allowing for another, are measured by the reduction in deviance (effectively equivalent to a chi-square test) obtained by estimating the effect of a factor, or of a second factor when the first has been allowed for.

CHAPTER 4

CLUSTERING OF CHILDHOOD CANCER IN GREAT BRITAIN: SPATIAL AND SPACE–TIME CLUSTERING

Introduction

4.1 One of the striking features of childhood cancers, particularly leukaemia, has been the observations of apparent case excesses near to a few nuclear installations and other industrial features (eg railways). This report is largely a consequence of the investigations of one such cluster of cases near Sellafield and other subsequent observations (Draper et al, 1993; COMARE, 2002).

4.2 These types of cancer clusters describe events which have already occurred (*post hoc* clusters) and their investigation has been hampered by a lack of knowledge as to how the cancers occur generally within our communities. For example, if the vast majority of cases are scattered randomly within our population, just one *post hoc* cluster could be very unusual. If, however, the cases not infrequently occur closer together, the interpretation of the existence of one *post hoc* cluster would be modified, in that it could, indeed, be one of these 'naturally' occurring events.

4.3 There have been, particularly for childhood leukaemia, many investigations both of *clustering* as a general phenomenon and of individual *clusters*. 'Clustering' has been defined (for example, in Gail and Benichou, 2000) as 'The irregular grouping of cases of disease in space or time or simultaneously in space and time'. This chapter is concerned solely with analyses of *clustering,* either space or space–time for the reason given in Chapter 1.

4.4 Broadly speaking, a rare cancer (such as the childhood cancers) could occur in the general population in several quite different scenarios.

i. The condition could occur quite randomly within the whole population showing no particular excesses in particular places or at particular times. This random distribution is the yardstick against which other possibilities are tested.

ii. The condition is clustered in time only, ie occurs more often in a limited time window of a few months or years and then the disease reverts to its original rate. This phenomenon would be universal geographically. This temporal clustering (which is typical of infectious diseases) is not expected for any childhood cancer and has never been reported in the literature; it is not investigated in this report.

iii. The condition, over lengthy period(s) of time, shows a propensity to occur more often amongst people living in certain small areas than would normally be expected by chance. This is spatial clustering and is examined further in this chapter. Spatial clustering may be evident over the whole time period covered by this report, with some small areas having permanently high rates of disease; alternatively, the high rates may be of somewhat shorter duration. We note that Sellafield and Dounreay have reported prolonged excesses in incidence but of different duration.

iv. The condition occurs more frequently near other cases in both space (as above) but also in relatively short periods of time (often within a few years or a few months). This is space–time clustering and is examined further in this chapter.

4.5 It is also quite possible to construct other situations, which are mixtures of these four possible scenarios, but for the purposes of this chapter spatial and space–time clustering are kept separate, with a view to comparing and contrasting their results.

Disease clustering and clusters

4.6 In order to investigate the natural distribution of childhood cancers a novel approach has been adopted. All cases of the condition have been examined over a predefined period of time and space. This is the search for case clustering. Because there are different possible outcomes of such an investigation (see paragraph 4.4) different methods have been created to address them.

4.7 There are various methods of identifying and interpreting the phenomenon of clustering and there is still uncertainty about which methodologies are to be preferred in different circumstances. The methods applied in this chapter are well known and have been employed extensively in

Prior hypotheses

In order to clarify what might be achieved by analysing the data for both spatial and space–time clustering, it is useful to have some prior hypotheses available based on the current literature. This is touched upon in Chapter 2, where sources of further reading may be found.

The main hypotheses are:

- Childhood leukaemia will show clustering, both spatial and space–time. This will be most marked for acute lymphoblastic leukaemia (ALL) and for the childhood peak (taken here as ages 1–4 years). Clustering will, however, involve older cases in the same areas as aggregations of younger cases.
- Places where clustering occurs may persist over lengthy time periods; thus 'between time-period' spatial clustering will be significant for consecutive time periods of, say, five or ten years.
- Hodgkin lymphoma diagnosed in younger children (aged 0–9 years), but not older children will show clustering but the locations of the clustering will change with time; this may be exhibited as spatial clustering over relatively short periods of time and/or space–time clustering.
- Cases of CNS tumours and soft-tissue sarcomas will show clustering. (The supporting literature focuses on space–time clustering but provides no justification for predicting that only this type of clustering will occur.)

The underlying reasons for the first two hypotheses lie in the concept that infectious agents (or, possibly, other environmental agents) may be involved in the aetiology of childhood leukaemia (see Chapter 2) and, for the second hypothesis, the lengthy period of excess incidence reported for Sellafield and to a lesser extent for Dounreay. The third hypothesis is based on the association between younger cases of Hodgkin lymphoma and Epstein-Barr virus infections. Finally, the newly recognised possibility that other childhood cancers may exhibit similar patterns of occurrence as the leukaemias (see Chapters 2 and 3) suggests that other childhood cancer will exhibit some form of clustering.

other studies. Whatever methods are used, it is important for the unbiased identification of generalised clustering that they are applied to the study of all cases occurring over a reasonably large geographical area and/or time interval. (By contrast, the study of individual 'clusters' – aggregations of cases that seem unlikely to have occurred by chance – is often initiated as a result of public or media concern and does not generally lead to valid statistical analysis.) It is also important that a single high quality source of data is used.

4.8 Paragraphs 4.12–4.32 examine clustering in space, ie the extent to which there is a tendency for cases of childhood cancer to be closer together when diagnosed than would be expected with a uniform risk (ie the same risk to each member of the population). The method used is based on an examination of the observed numbers of cases in the small areas corresponding to the census wards, which were also used in Chapter 3 of this report. In the absence of clustering, cases in any given area may be supposed to occur at 'random': the number would fluctuate around an 'expected number' calculated by applying national rates to the population count and allowing for known risk factors. The statistical variation around this is described by the 'Poisson distribution'. (See the glossary for more information on modelling and the nature of Poisson distribution.) One mechanism resulting in a deviation from this kind of randomness consists simply of a variation of risk between the different areas: we refer to this as heterogeneity of risk and speak of the heterogeneity of the resulting incidence rates. Other possibilities might include the occurrence of disease in small clusters within a particular area in such a way that the distribution followed is not the Poisson distribution, even though the mean (or average) rate of the distribution might be the same. Such a distribution would have variability larger than that occurring with the Poisson distribution (for which the variance is always equal to the mean). Such a distribution is said to be *over-dispersed* relative to the Poisson distribution and the phenomenon is often referred to as 'extra-Poisson variation' (EPV). The test employed to find extra-Poisson variations in paragraphs 4.12–4.32 is that due to Potthoff and Whittinghill (1966). The methods used in the section are further discussed in Annex 4A.

4.9 Paragraphs 4.33–4.45 consider space–time clustering, which is said to occur when cases appear in aggregations simultaneously in time and space in a way that cannot be explained by their distributions in space or time separately. Space–time clustering represents a departure from what would be predicted from knowledge of *where* cases live throughout the time considered and of *when* they occur over the whole area. Such clustering might arise, for example, from a small number of locations experiencing a substantially increased incidence over short (but distinct) periods of time, or from a larger number of shorter time periods with moderately increased incidence at limited locations.

4.10 The method of detecting space–time clustering used in paragraphs 4.33 to 4.35 is different from that used for spatial clustering. It compares the number of pairs of cases that occur close to one another in both space and time, which in the absence of clustering could be predicted from the number of pairs close in space and the number of pairs close in time. The original method is due to Knox (1964) and here it has been modified by the use of '*K*-functions', as proposed by Diggle et al (1995), the main purpose of this modification being to avoid the need to prescribe precisely what is meant by 'close' in space or time. The methodology is further described in Annex 4A.

4.11 The figure shows the different types of clustering. In order to get simple two-dimensional plots we have supposed that 'space' is just one-dimensional which is merely a necessary simplification (as if location were

something like 'number of miles from London in a north–south direction'). Several points need to be emphasised:

i. All of these have a random distribution of points; those with clustering have a large number (close to 50%) of the total points generated under the assumption of there also being a spatial cluster, a temporal cluster, or a space–time cluster. Thus each just shows one cluster.

ii. The number of points in these clusters is vastly more than we should expect in any distribution of childhood cancer cases.

iii. These plots are initially based on 'a uniform underlying distribution'. That is, each position in the rectangle is equally likely to have a point allocated to it. This would correspond to the unreal situation where people lived in housing units of equal size arranged uniformly over the whole geographical area. In real life the human population is clustered into towns and cities; thus even if every member of the population-at-risk has equal risk of disease (ie the distribution of cases is random) these cases are also clustered within towns and cities and eye-balling the map of cases shows apparent clusters.

iv. These plots also suppose that boundaries of clusters are parallel to the sides of the rectangles; this is a further simplification from the real-life situation where boundaries of census wards are complex and non-linear.

v. For all these reasons the plots suggest that detecting clusters is much easier than is in fact the case. This is why sophisticated statistical testing is required to detect clustering.

Spatial clustering

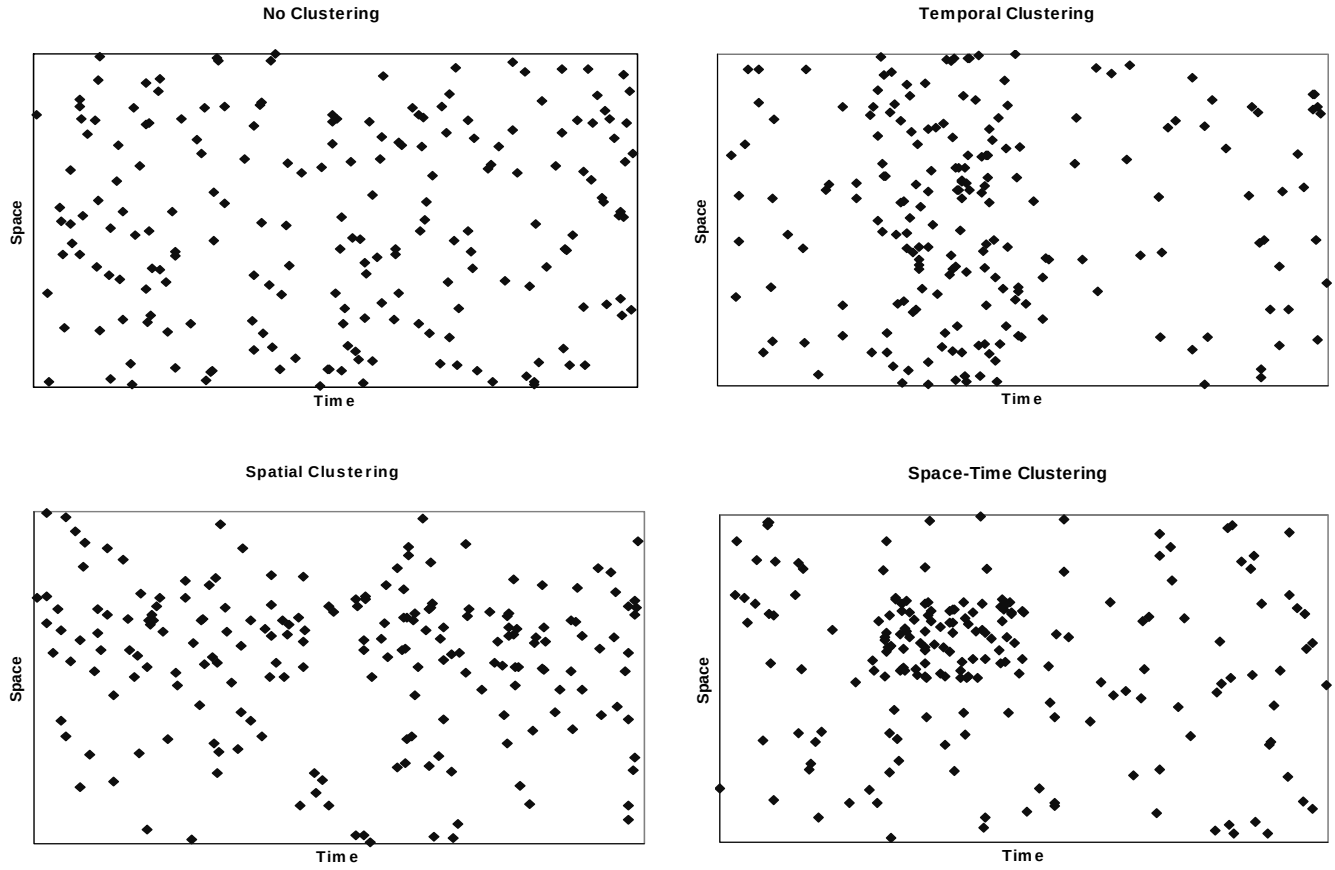
4.12 In the preceding chapter we presented data on rates of childhood cancer in different parts of Britain and described how these rates vary according to socio-demographic factors. This section focuses on the extent to which childhood cancer shows spatial clustering in small areas throughout Britain. The results from these analyses may help in interpreting reports of clusters in specific areas, such as those around certain nuclear installations.

4.13 In the preceding paragraphs we explained the concepts of disease clustering and of already defined or *post hoc* clusters, and distinguished between them. The size of the geographical area or the length of time over which cases might be investigated for possible clustering varies between studies. In this section, the focus is on the geographical aggregation of childhood cancer cases within census wards. These areas are relatively large compared with the highly localised areas that sometimes form the basis of cluster investigations (eg cases within a few streets of each other). However, data for wards have formed the basis of several investigations of childhood cancer rates around nuclear installations, including that described in Chapter 5 and the analyses of heterogeneity in rates discussed in Chapter 3.

Methods

4.14 The methods used for this analysis are based on the Potthoff-Whittinghill test (see the glossary and paragraph 4A.7 for more information). A byproduct of this approach is a parameter, beta (β), which measures the degree of extra-Poisson variation (EPV). Further details of the statistical methodology are given in Annex 4A. The parameter β can be split into subparts which numerically add up to β (eg representing effects within and between time periods) and hence the size of the two effects can be compared.

4.15 All the analyses have used age- and sex-specific census counts of the population interpolated for the intercensal years. Some of them have been replicated with adjustment for census measures of relevant socio-demographic factors, along the lines used in Chapter 3.



Types of clustering

Results

4.16 The major results are shown in Table 4.1. In these analyses twins and siblings have been included (see paragraph 4.21). The results show statistically significant evidence of clustering of ALL. A similar pattern was evident when children diagnosed under 1 year were excluded. When the test was applied to children aged 1–4 years at diagnosis, the clustering remained statistically significant. There was no evidence of clustering of ALL cases diagnosed over 4 years of age, and there was no evidence of clustering of this type for acute non-lymphocytic leukaemia (ANLL). Results for total leukaemia were driven by those for ALL.

4.17 There is no statistically significant evidence of clustering of the lymphomas *in toto* or of any subgroups. We cannot, however, conclude that clustering is absent for Hodgkin lymphoma (0–9 years) and non-Hodgkin lymphoma (0–9 years) since some shorter time periods (data not shown) show clustering of borderline statistical significance.

4.18 Leukaemia and lymphoma combined showed significant clustering during the period 1969–1993. This is likely to be driven by the results of ALL (paragraph 4.16).

4.19 There was *no* significant evidence for clustering of central nervous system tumours, bone tumours or for germ cell and related tumours.

4.20 There was significant clustering for soft-tissue sarcomas, renal tumours and ‘all cancers except leukaemia and lymphoma’ and for ‘all cancer’. It is not clear why ‘all cancers except leukaemia and lymphoma’ show clustering and this observation must be regarded as a novel finding.

Table 4.1 Results of analyses of extra-Poisson variation in childhood cancer rates by ward in Great Britain, 1969–1993

Diagnostic group	Age (years)	Cases	EPV[†]	90% CI[‡]	p-value[§]
ALL	0–14	8687	0.047	0.025–0.070	0.002 *
ALL	1–4	4441	0.030	0.008–0.053	0.015 *
ALL	5–14	3906	–0.002	–0.025–0.020	–
Leukaemia	0–14	10737	0.045	0.022–0.067	0.004 *
Leukaemia	1–4	5094	0.030	0.008–0.053	0.02
Leukaemia	5–14	5092	–0.008	–0.031–0.015	–
Leukaemia and lymphoma	0–14	13779	0.042	0.019–0.065	0.001
HL	0–9	487	–0.015	–0.038–0.008	–
HL	0–14	877	0.007	–0.016 – 0.030	–
NHL	0–9	1027	0.020	–0.003–0.043	0.08
NHL	0–14	1678	0.014	–0.009 – 0.036	–
CNS	0–14	7473	0.001	–0.022–0.023	–
Soft-tissue sarcomas	0–14	2101	0.026	0.003–0.048	0.04
Bone tumours	0–14		0.008	–0.015–0.030	–
Wilms' and other renal tumours	0–14	1890	0.036	0.013–0.059	0.007
All cancers except leukaemias and lymphomas	0–14	18278	0.039	0.017–0.062	0.004
All cancers	0–14	32323	0.075	0.052–0.097	0.0005

[†] Extra-Poisson variation as a proportion of Poisson variability.
[‡] Confidence interval.
[§] Monte-Carlo one-sided p-value for EPV>0 derived from 1000 simulations except where indicated (*=10,000); omitted if p> 0.1.

4.21 In these analyses consideration has to be given to the possibility that apparent aggregations of cases are attributable to the fact that twins or siblings living at the same address are both affected by malignant disease. It is known that co-twins of children with leukaemia, particularly at young ages, have a greatly increased risk of also being diagnosed with leukaemia. It also seems likely that this applies to other diagnostic groups; siblings of children with malignant diseases also have a higher (perhaps doubled) risk of being affected. Therefore, results have been confirmed by repeating the analyses with one of each pair of twins or siblings excluded (in any analysis for which both were eligible and resided in the same ward at diagnosis). This had very small effects on most of the results. However, significant evidence of clustering for retinoblastoma can be attributed to twins and siblings (data not shown), which is not surprising.

4.22 The analyses reported in Table 4.1 were repeated with adjustments for region and socio-economic factors (the expected numbers allowed for these large-scale variations). The adjusted and unadjusted analyses show very similar results.

4.23 Tables 4.2, 4.3 and 4.4 grouped the results by time periods, age groups and diagnostic groups, respectively. In each case analyses examine the possibility of clustering within each pre-specified grouping (ie within time periods, etc). In addition, the analyses take each group as a whole to determine

whether there are differences in the magnitude of clustering between groups (ie between time periods, etc). Table 4.2 distinguishes the 'between-time-period' and 'within-time-period' clustering that has been demonstrated for leukaemia and lymphoma over the total time period. What is important to note here is that the between-time-period clustering is statistically significant for both age groups when time periods are split into five-year intervals and for the total age range when ten-year intervals are analysed. This points to aggregations within wards, which persist over time, especially when the broad age range is analysed. Similar analyses, applied to other diagnostic groups failed to show this phenomenon, which is illustrated in the table by Hodgkin lymphoma.

Table 4.2 Between-time-period and within-time-period contributions to extra-Poisson variation

Diagnosis	Age (years)	Time periods	β-within† (p-value)‡	β-between§ (p-value)‡
ALL	1–4	5 x 5 year periods	0.0058	**0.0246 (0.0295)**
ALL	0–14	5 x 5 year periods	**0.0107 (0.0465)**	**0.0365 (0.0025)**
ALL	1–4	2 x 10 year periods	**0.0216 (0.0115)**	*0.0125 (0.0925)*
ALL	0–14	2 x 10 year periods	0.0067	**0.0319 (0.0015)**
HL	0–9	5 x 5 year periods	0.0058	–0.0207

Note: Bold typeface indicates statistically significant results, whilst results in italics are based on small numbers and are hence unreliable.
† Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates within the time periods stated.
‡ The p-values are based on 1000 Monte-Carlo simulations and are omitted when p>0.1.
§ Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates between the time periods stated.

Table 4.3 Between-age-group and within-age-group contributions to extra-Poisson variation, 1969–1993

Diagnostic group	Age group (years)	β-within† (p-value)‡	β-between§ (p-value)‡
ALL	0–4, 5–14	**0.0173 (0.0465)**	**0.0301 (0.0005)**
HL	0–9, 10–14	0.0041	0.0030
All cancers other than leukaemia and lymphoma	0–4, 5–14	**0.0248 (0.0035)**	*0.0146 (0.0775)*

Note: Bold typeface indicates statistically significant results, whilst results in italics are based on small numbers and are hence unreliable.
† Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates within the age periods stated.
‡ The p-values are based on 1000 Monte-Carlo simulations and are omitted if p>0.1.
§ Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates between the age periods stated.

Table 4.4 Between-diagnostic-group and within-diagnostic-group contributions to extra-Poisson variation, 1969–1993

Diagnostic group	β-within† (p-value)‡	β-between§ (p-value)‡
ALL; other leukaemias	**0.0238 (0.0095)**	**0.0209 (0.0215)**
Leukaemia and lymphoma; all others	**0.0406 (0.0005)**	**0.0341 (0.0005)**

Note: Bold typeface indicates statistically significant results
† Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates within the age periods stated.
‡ The p-values are based on 1000 Monte-Carlo simulations and are omitted if p>0.1.
§ Extra-Poisson variation as a proportion of Poisson variability, based on variation in rates between the diagnostic groups stated.

4.24 Table 4.3 shows analyses for within age group and between age group for the whole time period. The between-age-group component was somewhat large and more significant for ALL, especially when the ages were grouped into 0–4 and 5–14 years as shown in this table. For other cancers (ie all except leukaemia and lymphoma), the within-age-group contributions to EPV were significant, and a similar situation was suggested for non-Hodgkin lymphoma but was not statistically significant (not shown). In contrast, for Hodgkin lymphoma, neither the between- nor within-age-group components approached statistical significance.

4.25 Table 4.4 summarises analyses of the extent to which excesses of different types of childhood cancer arise in the same area, by looking at the components to EPV both between and within diagnostic groups. There is evidence of a substantial between-diagnosis-subgroup component for ALL and 'other leukaemias'.

4.26 Table 4.4 also shows that leukaemia and lymphoma when taken with all other cancers had a statistically significant EPV between-diagnostic-group component. We attempted to identify other diagnostic groups which tended to aggregate but the results were inconclusive.

Discussion

General considerations

4.27 In interpreting these results, it should be pointed out that the Potthoff-Whittinghill test seeks evidence of heterogeneity of cancer rates between census wards. In particular, individual clusters will influence this test only if they fit within the ward boundaries and form a substantial proportion of cases in the wards concerned.

4.28 The analyses based on adjusted expected numbers do not indicate that the extra-Poisson variation is attributable to systematic variation associated with socio-demographic factors that are already known to influence incidence rates. In addition, the influence of twins and siblings has been considered and appears not to affect the results, with the exception of those for retinoblastoma (see paragraph 4.21). It is possible that associations with other unmeasured factors provide an explanation of more of the extra-Poisson variation, ie that there are socio-demographic factors that vary between wards and are associated with the probability of developing childhood cancer. However, at present, a likely explanation is that the risk is due to real but unknown differences between wards and is not the result of random demographic differences.

Leukaemia

4.29 The magnitude of the extra-Poisson variation (at 4.5%) for leukaemias is of the same order as, but larger than, that reported in the EUROCLUS project (1.7%), based on data from various European countries, including Britain (Alexander et al, 1998). The results for ALL and all leukaemias combined, including the focus on the childhood age peak, are consistent with the literature (see Chapter 2) and with our prior hypotheses. In common with EUROCLUS, the data for ALL point to aggregations of cases arising in the same areas at different ages; in particular, at 1–4 years and 5–14 years. This is despite the fact that cases of ALL aged 5–14 years do themselves not display statistical significance, nevertheless it is possible that some older cases can aggregate with more frequent younger ones.

Lymphomas

4.30 We found no statistically significant evidence of clustering of Hodgkin lymphoma or of non-Hodgkin lymphoma. Statistical power is, however, limited, but the result for Hodgkin lymphoma is contrary to our prior hypothesis.

Other cancers

4.31 The statistically significant extra-Poisson variation for 'cancers other than leukaemia and lymphoma' and for all cancers is surprising. The limited evidence for extra-Poisson variation between diagnostic groups and between age groups for the other cancers suggests that some small areas have excesses of distinct diagnostic groups.

4.32 This analysis shows, for the first time, evidence that childhood cancers combined cluster spatially, according to residence at time of diagnosis. This may point to more similarity in the aetiologies of (some of) these diseases than is currently accepted. However, due to the fact that this is a new observation, this result must be treated with caution.

Summary of results of spatial clustering

We summarise here the main findings concerning clustering for selected diagnostic groups, subgroups by age, and combinations of diagnostic groups.

- The analyses showed statistically significant evidence of weak clustering for acute lymphoblastic leukaemia (ALL) over the whole age range and the childhood peak (1–4 years)
- There was a significant clustering for all cancers combined and for the group consisting of all cancers other than leukaemia and lymphoma.
- Soft-tissue sarcomas and Wilms' tumours showed significant clustering.
- Clustering of leukaemia tended to persist across the entire time period, ie the same small areas showed excesses over time periods longer than five years or even ten years, ie between periods.
- There was clustering between age groups (ie aggregations of cases involving more than one age group) for ALL but not for other leukaemias or lymphoma. This, however, might have involved some examples of older cases in areas with two or more younger cases since spatial clustering of older cases of ALL was not observed.
- The results could suggest greater commonality of aetiological factors for all childhood cancers than had been suspected previously.

Space–time clustering

4.33 The space–time analyses complement the spatial clustering analyses. The aims of the study were to investigate the specific prior hypotheses. The joint interpretation of spatial and space–time clustering of childhood cancer is presented in paragraphs 4.46–4.59.

Data

4.34 Analyses in the present section are based on cancer registration data during 1969–1993, provided by the Childhood Cancer Research Group (CCRG) – the same data as have been used throughout this report.

4.35 For each case of childhood cancer, the home address at the time of diagnosis was postcoded and the Ordnance Survey 100-metre grid reference associated with that postcode attached. Since a postcode is an areal unit, a single point grid reference will only give an approximation of the location of a given address within a postcode. The grid reference that is allocated to a postcode is the southwest corner of the 100-metre grid square which contains the first address in that postcode. Hence each grid reference of the address at diagnosis allocated via the postcode will be accurate to within approximately

100 metres in the easting parameter and 100 metres in the northing parameter, though this will vary according to the size and shape of the postcode and the distribution of residencies within it. Before these grid references were disseminated to research workers, the coordinate axes were shifted and rotated to preserve confidentiality of location without detriment to the analysis.

Methods

4.36 The space–time interactions between times and places of diagnosis were examined. The analyses presented are based on *K*-functions. *K*-function analysis may be regarded as a generalisation of the Knox test (Knox, 1964). The Knox test regards a pair of cases as being in 'close proximity' if they are diagnosed at addresses which are close both in space (less than *s* km apart, where *s* can be any small number) and at times which are close (less than *t* months apart, where, for example, $t = 12$ or other small number). However, the Knox test uses an arbitrary choice of critical values to define 'close proximity' (*s* and *t*). A simplification of a procedure due to Diggle et al (1995) is used to overcome the problem of arbitrary critical values. Space–time clustering occurs when the test shows that there are significant excess numbers of cases in 'close proximity'.

4.37 It is possible that geographical distance may be inappropriate as a measure of closeness, especially when both urban and rural areas are included in the study. Any specified distance between two cases may have different meanings in urban and rural areas where, for example, sizes of school catchment areas differ. We therefore feel it is appropriate to examine the influence of population density on any clustering effect (see Annex 4A, paragraphs 4A.22 and 4A.23).

4.38 An implicit assumption that is made when fixed geographical distance thresholds are used is that the underlying population distribution is uniform. The number of cases expected to be close in space is calculated under this assumption. Hence, the use of fixed geographical distance thresholds may inflate apparent clustering effects in more densely populated areas (by underestimating the number of cases expected to occur in a localised area) and deflate apparent clustering effects in less densely populated areas (by overestimating the number of cases expected to occur in a localised area). The nearest neighbour (NN) (see the glossary) threshold method overcomes such potential anomalies by taking localised variations in population density into account. Furthermore, use of NN thresholds better reflects the possible opportunity for person-to-person contact (eg via school attachment areas which will be larger in more rural areas and smaller in more urban areas). Thus, it is also a better method for testing prior hypotheses that relate to an infectious aetiology (see also paragraphs 4A.22 and 4A.23). Statistically significant results from this method are highlighted in this section. Statistical significance in all analyses was taken as $p<0.05$.

Results

4.39 Table 4.5 presents detailed results from the analyses. In all analyses twins have been excluded.

4.40 A number of pre-specified diagnostic and age subgroups were analysed. These correspond very closely with the groups considered in paragraphs 4.12–4.32.

4.41 The results show statistically significant evidence of space–time clustering of acute lymphoblastic leukaemia. When the test was applied to children aged 1–4 years at diagnosis, results remained statistically significant. There was no evidence of space–time clustering of acute lymphoblastic leukaemia cases diagnosed over five years of age or for acute non-lymphocytic leukaemia (ANLL). Results for total leukaemia were statistically significant but at a weaker level.

Table 4.5 Main results of analyses of space–time clustering in childhood cancer in Great Britain, 1969–1993[†, §, ¶]

Diagnostic group	Age (years)	NN threshold[‡]	
ALL	0–14	p=0.04*	(*S*=1.3%)
ALL	1–4	p=0.03*	(*S*=4.1%)
ALL	5–14	p=0.44	
Leukaemia	0–14	p=0.048*	(*S*=0.2%)
Leukaemia	1–4	p=0.16	
Leukaemia	5–14	p=0.31	
HL	0–9	p=0.11	
HL	0–14	p=0.13	
NHL	0–9	p=0.39	
NHL	0–14	p=0.09	(*S*=9.8%)
CNS	0–14	p=0.41	
Soft-tissue sarcomas	0–14	p=0.03*	(*S*=9.8%)
Bone tumours	0–14	p=0.08	
Wilms' and other renal tumours	0–14	p=0.23	
Osteosarcoma	0–14	p=0.02*	(*S*=25.5%)
Astrocytoma	0–14	p=0.06	
All cancers except leukaemia and lymphoma	0–14	p=0.12	
All cancers	0–14	p=0.22	

* Statistically significant level at the 5% level.

† Cases are close in time if dates differ by $<t$, where t is in the range 0.1–1.5 year (see paragraph 4A.17).

‡ Cases are close in space if either is within the distance to the Nth nearest neighbour of the other (in the total dataset), where N is in the range 19–33.

§ The p-value is obtained by simulation with dates randomly re-allocated to the cases in the analysis (see paragraph 4A.19).

¶ Nearest neighbour (NN) threshold cases are defined as being close in space and if the location of one (or both) of each pair examined were nearer than the other's 26th NN in the total dataset of that diagnosis.

Strength (S) = [(Observed – Expected) / Expected] × 100 counts of pairs which are defined by the test as being close in time and space.

4.42 There was statistically significant evidence for space–time clustering of soft-tissue sarcomas and osteosarcoma.

Discussion

4.43 It is interesting to note that space–time clustering for leukaemias (particularly acute lymphoblastic leukaemia), and soft-tissue sarcomas was also found in North West England, from 1954 onwards (Birch et al, 2000; McNally et al, 2002b, 2003b), albeit for soft-tissue sarcomas in relation to birth details (1954–1998). However, when the North West England data were analysed separately from the rest of the dataset it was found that the clustering occurred elsewhere and not in a more limited time period (1969–1993) for North West England (R McNally, personal communication). The previous finding of space–time clustering for childhood leukaemia was most marked for cases

of ALL in the childhood peak for the period 1954–1985 and based on time of diagnosis and place of birth, but was also present using time and place of diagnosis (Birch et al, 2000). For the latter time period (1980–2001) space–time clustering of childhood leukaemia was confined to cases of precursor B-cell ALL in the childhood peak and was only present using time and place of birth (McNally et al, 2002b). The finding of space–time clustering for soft-tissue sarcomas was only present based on time and place of birth and was not found based on time and place of diagnosis (McNally et al, 2003b).

4.44 The finding of space–time clustering for osteosarcomas had not previously been shown in the North West England data, from 1954 onwards (McNally et al, 2003b).

4.45 There was statistically significant space–time clustering for cases of all types of leukaemia, aged 0–14 years as a whole. This was attributable to statistically significant space–time clustering for cases of ALL, but not for cases of ANLL (which were of borderline significance). Furthermore, the space–time clustering was only found for cases of ALL aged 1–4 years. The lack of clustering for all leukaemias aged 1–4 years can be explained by the diluting effect of non-clustering cases of ANLL.

Summary of results of space–time clustering

- The analyses showed statistically significant evidence of space–time clustering for acute lymphoblastic leukaemia at ages 1–4 years and over the whole age range but not for 5–14 years. There was weaker evidence for space–time clustering in the total leukaemias.
- Soft-tissue sarcomas and osteosarcoma showed statistically significant evidence of space–time clustering.

Bringing the results together

4.46 We should like to emphasise that a large number of statistical tests have been applied in the preceding sections of this chapter. Since there is a substantial amount of dependence between them it is not easy to estimate how many 'statistically significant results' would arise by chance alone (ie if the distributions were in fact random). At least some of the positive results presented here may be due to this effect. It is therefore essential for readers to exercise caution in interpreting individual results. Those which are most likely to be genuine are those with a high level of statistical significance, with support in related analyses, biological plausibility and with the findings supported elsewhere in the literature.

4.47 On the other hand, a cautious interpretation of negative results is also required. It is, for example, inappropriate to conclude that since one diagnostic group does not display clustering then infections or environmental risk factors do not contribute aetiologically. Infectious agents can be involved in the causation of cancers without there being evidence of clustering, this can arise when the relevant agent does not itself cluster (eg if it is endemic); Epstein-Barr virus as a cause of Burkitt's lymphoma in sub-Saharan Africa is a well-documented example – where clustering is only evident when a co-factor which does cluster is involved (eg malaria).

4.48 In addition, attention to latency is very important. Since all the analyses in this report use the location at diagnosis there is an implicit

assumption that the majority of cases were in the same locations at diagnosis as when relevant causative exposures occurred. If the time gap between the exposures and diagnosis is large then this assumption becomes less tenable. As a result, genuine effects will be diluted in the analyses.

4.49 In general, if exposure to one or more infectious agents contributes positively to the aetiology of cancer then we should predict that space–time clustering and spatial clustering will be observed. However, a number of caveats are appropriate. Space–time clustering (as here, using location at diagnosis) will only be strongly identified if the latent period is short (or at least relatively constant). This would be the case if an infection contributes to the later genetic events and if the infectious agent itself shows an epidemic pattern. If all these apply then we predict that space–time analyses are powerful enough to detect evidence of clustering. Spatial clustering, on the other hand, can cope with variation in latent period and infections contributing to earlier genetic events. In all of the above, 'infectious agents' can be replaced by 'other environmental agents localised in space (spatial clustering) or in space and time (space–time clustering)'.

4.50 Although we have placed importance on exposure to infection, others have focused on local variations in risk due to environmental pollutants. As we have noted above, all results of spatial clustering given here are capable of being interpreted this way; positive results for space–time clustering are less likely to be linked to environmental phenomena unless the environmental exposures are transient and the latent periods short (or at least relatively constant).

Key results and interpretation

4.51 The results (see Tables 4.1 and 4.5) show considerable agreements between the two distinct methods. Specific forms of leukaemias, soft-tissue sarcomas and 'all cancers other than leukaemia and lymphomas' all demonstrate both spatial and space–time clustering. Likewise, other major groups of specific childhood cancers such as CNS tumours show neither spatial nor space–time clustering.

4.52 One exception is that Wilms' and other renal tumours show some spatial clustering but no space–time clustering.

4.53 Leukaemia shows significant spatial and space–time clustering; this is evident for analyses over the entire age range and for the younger children (1–4 years) but not those aged 5–14 years analysed separately. There is evidence of spatial aggregation involving children of different age groups. Overall the results can be interpreted as providing further evidence supporting an infectious aetiology rather than being linked to environmental pollution or other explanations. The observed pattern of occurrence is consistent with a number of previously isolated small areas having subsequent population mixing and consequent increases in infections; one or more of the agents might result in a leukaemia risk as a rare consequence of that particular infection (see Chapter 2). The results suggest that the same exposures may contribute to cases of older children but with different (presumably longer) latent periods.

4.54 These results are driven by those for acute lymphoblastic leukaemia. The persistence of spatial clustering over time, and the emphasis here on the entire age range, could be interpreted as evidence that the same exposures may contribute to cases in older and younger children with different latent periods.

4.55 Hodgkin lymphoma shows no significant evidence of clustering. This remains true when the younger children (0–9 years) are considered separately.

We have already observed that negative results should not be over-interpreted; other data suggest that younger Hodgkin lymphoma cases are linked with Epstein-Barr virus infection.

4.56 Cancers other than leukaemia and lymphoma show significant spatial and space–time clustering. In the spatial analysis, these cases aggregate with leukaemia and lymphoma. This provides the basis for an argument that there are shared aetiological agents or shared risk-promoting demographic/ immunological circumstances between the haematopoietic and other childhood cancers. It also could suggest that latent periods differ by diagnosis.

4.57 Soft-tissue sarcomas show significant spatial and space–time clustering. Such a pattern of occurrence may well be explained by an infectious agent or agents. We note that the herpes virus HHV8 is causally associated with an adult soft-tissue sarcoma in people with immune impairment (see Chapter 2).

4.58 Both Wilms' tumours and osteosarcomas show some (weak) sign of clustering, the significance of this is unknown. However, CNS tumours show no significant evidence, in these data, of any form of clustering.

4.59 In summary, the concordance in results between two distinct statistical approaches gives some confidence to the prior hypothesis that childhood leukaemia clusters (particularly the childhood peak of ages 1–4 years). The prior hypotheses not supported by these data relate to Hodgkin lymphoma and CNS tumours which do not show clustering.

ANNEX 4A

DATA AND METHODOLOGY

Spatial clustering

Data

4A.1 Analyses in the first part of the present chapter are based on data on cancer incidence during 1969–1993, provided by the Childhood Cancer Research Group (CCRG) for 10,440 small areas. These areas are based on 1981 census wards for England and Wales, and corresponding areas in Scotland. The data are identical to those used elsewhere in this report.

4A.2 For each ward person-years by sex and age group (<1, 1–4, 5–9 and 10–14 years) were estimated using population data provided by the CCRG from each of the 1971, 1981 and 1991 censuses. These data were based upon the 1981 census ward boundaries and numbers for intervening years were estimated by linear interpolation between the censuses.

4A.3 Postcode grid references of the address of each case at the time of diagnosis allowed spatial referencing of the address at diagnosis to within about 100 metres for the easting and the same for the northing.

4A.4 Expected numbers of cases for each small area were computed by applying overall age- and sex-specific rates for the relevant time period to the person-years at risk in each small area. However, the leukaemias and certain other subgroups show significant evidence of heterogeneity by region and by area-specific socio-economic status (see Chapter 3). Therefore, *a priori* it is possible that heterogeneity between wards is merely a consequence of associations with these larger-scale factors. In order to check whether this was true, a second set of expected numbers has been derived by fitting a regression model containing terms for region and for socio-economic status. Little difference in the results emerged; the results of these adjusted analyses are not shown in detail but are commented upon in the text.

4A.5 It should be appreciated that the expected numbers of cases in individual wards are generally very small, so that the total number of cases is spread very thinly, even for the largest tumour group. This is illustrated in Table A.1, the first column of which shows the numbers of wards analysed in Tables 4.1–4.4. These numbers differ slightly between different age groups because of wards in which there are no children at risk at particular ages, such wards being excluded from the respective analyses. Table 4A.1 also shows, for each tumour group, the numbers of wards where the numbers of cases were (a) greater than zero and (b) greater than one; the relevance of the latter is that only wards with more than one case observed make a contribution to the Potthoff-Whittinghill statistic. Also given are the total numbers of cases and the largest and smallest expectations of cases per ward. Although the very small numbers of cases in some of the datasets mean that tests based on normal approximations are likely to be unreliable, this should not affect the p-values in Tables 4.1–4.4, since these were calculated by simulation methods, which return unbiased estimates of the true p-values.

Table 4A.1 Summary statistics for the observations and expectations over the years 1969–1993

Diagnostic group	Age (years)	No. wards	No. wards with obs>0	No. wards with obs>1	Total obs	Max exp	Min exp
ALL	0–14	10418	4959	2211	8687	6.86	0.00043
ALL	1–4	10412	3218	929	4441	3.7	0.00042
ALL	5–14	10418	2963	710	3906	3.02	0.00014
Leukaemia	0–14	10418	5565	2759	10737	8.48	0.00053
Leukaemia	1–4	10412	3541	1122	5094	4.24	0.00049
Leukaemia	5–14	10418	3598	1062	5092	3.94	0.00018
Hodgkin	0–9	10417	470	17	487	0.4	0.00002
Hodgkin	10–14	10413	820	53	877	0.67	0.00006
NHL	0–9	10417	941	78	1027	0.84	0.00004
NHL	10–14	10413	619	31	651	0.5	0.00005
CNS	0–14	10418	4572	1830	7473	5.9	0.00037
Soft-tissue sarcomas	0–14	10418	1787	268	2101	1.66	0.00010
Renal	0–14	10418	1604	247	1890	1.49	0.00009
Other cancers	0–14	10418	7114	4479	18278	14.44	0.00090

Statistical methodology

4A.6 There has been a large amount of research in recent years into statistical methods for identifying localised clustering of disease. Alexander and Boyle (1996) have compared different methods, using simulated data for census wards. The results described in this chapter are based on the Potthoff-Whittinghill test (Potthoff and Whittinghill, 1966; Muirhead and Butland, 1996), which is described further below. This approach was used previously in the EUROCLUS project, based on childhood leukaemia incidence data from various European countries (Alexander et al*,* 1998).

4A.7 In the absence of clustering, the observed number of cancer cases in a geographical area should follow a Poisson distribution with mean equal to the expected number of cases in that area. If this were so, then the variance of the observed number of cases would equal the expected number of cases. The Potthoff-Whittinghill test is used to test whether the ratio of the variance to the expected number is greater than one. If it were, then the data would be over-dispersed relative to the Poisson distribution and relatively large or small numbers of cases would arise in some areas more often than predicted under the Poisson distribution. In such circumstances clusters may be seen, but they may represent a general feature of the distribution of the disease, rather than being confined to specific locations such as nuclear installations.

4A.8 The magnitude of any over-dispersion can be quantified as a factor by which the variance of the observations is increased. In our analyses we have represented this factor by the quantity $(1 + \beta)$ and defined β as the extra-Poisson variation (EPV). Thus EPV = β would equal 0.1 if the variance of the theoretical distribution of the number of cases in each ward were 10% larger than predicted (in Table 4.1) by the Poisson distribution. Tables 4.1–4.4 give values of β together with 90% confidence intervals based on a normal approximation to its distribution. Formulae for β and its standard error may be found in Muirhead and Butland (1996). Because this approximation may not be

very good in small datasets, the p-values in the Potthoff-Whittinghill test were estimated by simulation. Estimating significance tests and confidence intervals in different ways means the results do not always appear to correspond. Where there is a discrepancy between the results of these tests and the confidence intervals, the former should be regarded as more reliable.

4A.9 Additional analyses split the EPV between and within subgroups, which were classified by time of diagnosis (both for five periods each of five years, and for two periods of ten years), age at diagnosis and diagnostic subgroup. For the latter analysis, selected broad groups of diagnoses were considered and subsequent analyses were driven by results for these. The methodology here is that described in Alexander et al (1998), and derived from Muirhead and Ball (1989).

Space–time clustering

Data

4A.10 The dataset used for the space–time clustering analyses was identical to that used for the spatial clustering and for other analyses in this report. However, the analyses focus on the individual locations. As for the spatial analyses, these were obtained from postcodes to an accuracy of approximately 100 metres north and east. In order to preserve confidentiality, the grid references were given relative to axes that had been shifted and rotated by an undisclosed amount.

Statistical methodology

4A.11 The analyses presented are based on *K*-functions. *K*-function analysis may be regarded as a generalisation of the Knox test (Knox, 1964). For this reason the Knox test is outlined first of all.

4A.12 The Knox test regards a pair of cases as being in 'close proximity' if they are diagnosed both at addresses which are close in space (less than s km apart, where, for example, $s = 5$) and at times which are close (less than t months apart, where, for example, $t = 12$). These limits are arbitrary, but have been used in a number of other space–time clustering studies in parts of Great Britain (Birch et al, 2000; McNally et al, 2002a,b, 2003a, 2004).

4A.13 The number of pairs of cases that are in close proximity is calculated (O). The numbers of pairs of cases that are close in space (D) and that are close in time (T) are calculated. From these, and assuming that spatial and temporal proximity are independent, we have the expectation of O, the number of pairs of cases close both in time and in space, given by $D \times T / N$, where N is the total number of case pairs.

4A.14 If O appreciably exceeds E there is evidence of space–time clustering and statistical tests can determine whether this excess is statistically significant. The magnitude of the excess is estimated by $S = [(O - E) / E] \times 100$. The variability of S depends on E.

4A.15 A related quantity whose variability is approximately independent of E is $R = (O - E) / \sqrt{E}$.

4A.16 There are two problems with the Knox approach. First, boundary problems may be important since it can be difficult or impossible for a case near a geographical boundary or the end of a time interval to be close to as many cases as if it occurred near the centre. The second problem is the arbitrariness of the selected values (s and t).

4A.17 A simplification of a procedure due to Diggle (Diggle et al, 1995) is used to overcome the problem of arbitrary critical values. In our analyses, we performed a set of Knox-type calculations to obtain 225 values of R (see

paragraph 4A.15) by varying the critical values over a pre-specified set: for close times, t = 0.1, 0.2, …, 1.5 years and for close points in space, s = 0.5, 1, 1.5, …, 7.5 km.

4A.18 The test is then based on the observed value of the K-function, (K_O), which is formed by summing R over the pre-specified values of s and t.

4A.19 The distribution of the K-function is unknown and so must be estimated by simulation. For each simulation, the dates of diagnosis were randomly re-allocated to each of the cases in the analysis and a value of the K-function (K_s) was calculated from the simulated data. This was repeated for a total of n_{SIM} simulations. The observed value of the K-function, K_O, was compared with the simulated values, K_s (where s = 1, …, n_{SIM}). The p-values were estimated by calculating the proportion of the n_{SIM} simulations for which $K_s > K_O$. Hence statistical significance was assessed.

4A.20 The K-function analysis yields no measure of the magnitude of the effect. The p-values depend both on the magnitude and on the statistical power, which in turn depends on the number of cases. Therefore, in this report, the statistic S, defined in paragraph 4A.14 and obtained from the Knox test (with critical values taken as 5 km and 1 year), is provided as some indication of the magnitude. However, a small value of S may occur even when the true effect is large if the clustering occurs at a scale corresponding to critical values different from 5 km and 1 year.

4A.21 It is possible that geographical distance may be inappropriate as a measure of closeness, especially when both urban and rural areas are included in the study. We therefore feel it is appropriate to examine the influence of population density on any clustering effect.

4A.22 For a specific ‘index’ case, the other cases which were in closest proximity were termed ‘nearest neighbours (NN)’. These NN cases were ranked by their distance from the index case: 1, 2, 3, …. This was done for every case in the dataset in turn by treating it as an index case.

4A.23 On inspection of the whole set of nearest neighbour distances, it was observed that the average distance to the 26th nearest neighbour was about 5 km (though these distances varied greatly, between 245.3 km for a very isolated location to 0.7 km in a very densely populated location). Consequently, the distances to the Nth nearest neighbours (where N took the values 19, 20, 21, …, 33) were used instead of the distances previously considered (namely 0.5 to 7.5 km) (see paragraph 4A.17).

CHAPTER 5

INCIDENCE OF CHILDHOOD CANCER AROUND NUCLEAR INSTALLATIONS IN GREAT BRITAIN

5.1 In our Tenth Report (COMARE, 2005) we reviewed the earlier evidence relating to childhood cancer around nuclear installations in Great Britain but more importantly we presented new data to test whether claimed excesses of childhood cancer around nuclear installations are a regular feature of sites in Great Britain. These analyses are new, both in the sense that they use new data and because, for each site, a series of computations was carried out to determine the most appropriate statistical test. Readers interested in the detailed methodology are referred to the Tenth Report, but we wish these results to be considered alongside the other analyses here in our Eleventh Report. Therefore, in this chapter we reiterate the discussion and conclusions of our Tenth Report.

5.2 The main results from the latter report are reproduced in Tables 5.1–5.4. These tables give the basic statistics for each of the 26 sites analysed, specifically: the number of census wards within 25 km of the installation; the observed number of cases in these wards during the years 1969–1993; the number of such cases that would be expected using national rates, after adjustment for socio-demographic factors as described in Chapter 3 of this report; and the ratio of these two numbers, which is the standardised incidence ratio (SIR). The SIR, in detecting the excess of cases in the whole 25-km circle around each installation, is a rather blunt instrument for detecting an elevated risk close to it. Much methodological work has recently addressed the question of what test procedure might be better at identifying such an elevated risk. The problem is not straightforward, not least because the best test to use will depend on what alternative concentration is postulated (eg how closely the cases are concentrated to the centre of the circle). The arguments are discussed in the Tenth Report in some detail: an elaborate procedure was used that selected the test found to be best ('most powerful', in statistical terminology) for a postulated risk pattern that was a mixture of various plausible patterns. The last column of Tables 5.1–5.4 gives the results of this procedure as p-values, with the test actually selected being indicated in the penultimate column. Readers interested in more details of these tests and how the p-values were determined should refer to the Tenth Report. Suffice it to say that the analyses were informed by the precept that it is of considerable importance to use the best test procedure available, especially where the numbers involved are small, since this helps to ensure that significant results are genuine rather than spurious. The discussion which follows in this chapter refers implicitly to both the elevated risk, as indicated by the SIR, and also by the tests of spatial concentration reported in the tables.

Nuclear power stations

5.3 The results for nuclear power stations are unambiguous and, as might be expected from their very low discharges, there is no indication of any effect on the incidence of childhood cancer (see Tables 5.1 and 5.2). For leukaemia and non-Hodgkin lymphomas there were only three sites with marginally higher than expected numbers and ten where the numbers were less than expected. None of these was remotely significant from a statistical point of

view. For solid tumours, there were five sites with very slightly raised values and eight sites with lower values. Again, none of these exhibited statistical significance. Moreover, within the 25-km circles there was no evidence of any trend for rates to be higher nearer to the sites. We can, therefore, say quite categorically that there is no evidence from this very large study that living within 25 km of a nuclear generating site within Britain is associated with an increased risk of childhood cancer.

Other nuclear sites

5.4 The situation with the other nuclear sites is more complicated. For leukaemia and non-Hodgkin lymphoma (Table 5.3) there are four sites where there is some evidence of a raised incidence close to the installation, namely Sellafield, Burghfield, Dounreay and Rosyth. Each of these sites has been identified previously as having a possibly increased risk in the vicinity. The most important finding in this new analysis is that none of the other sites in this group has a significantly increased rate of leukaemia and non-Hodgkin lymphoma. Five of these other sites have registration rates slightly higher than the expected value, whereas six sites have slightly lower rates than this value.

5.5 For solid tumours (Table 5.4) four sites in this study stand out as having rates that are significantly raised, namely Aldermaston, Burghfield, Harwell and Rosyth. Excluding these, there are four with slightly raised rates (but well below statistical significance), and seven with slightly lower rates. None of these rates differs from the expected rates. We consider that there is no evidence to suggest that any of these sites, with the exception of Aldermaston, Burghfield, Harwell and Rosyth, is associated with raised rates of childhood solid tumours. It is interesting that Dounreay, with a documented increase in incidence of childhood leukaemia, has a markedly lower than expected rate for solid tumours (SIR 0.48). This rate is, however, based on only three cases (Expected=6.29) and is almost certainly a chance finding. It is noteworthy that two of the four sites with significantly raised rates for solid tumours also have significantly raised rates for leukaemia and non-Hodgkin lymphoma, namely Burghfield and Rosyth.

5.6 For Rosyth the pattern of incidence is significantly different from what would be expected, both for leukaemia and non-Hodgkin lymphoma and for solid tumours (Tables 5.3 and 5.4). However, these patterns are quite distinct for the two groups of cases. For solid tumours, there is an overall excess incidence in the 25-km circle (SIR=1.14). This appears to reflect a previously reported high incidence of CNS tumours (which make up a large component of the 'solid tumours' category) in the surrounding Fife and Lothian areas (McKinney et al*,* 1994; Sharp et al*,* 1999). For leukaemia and non-Hodgkin lymphoma on the other hand, there is no evidence of a substantially increased overall excess incidence in the 25-km circle (SIR 1.03), but there is a statistically significant tendency towards a higher incidence near the site than would have been expected. In previous studies, Heasman et al (1986a) reported a higher than expected incidence of leukaemia within 6.25 km of the site in 1974–1978, but not in the earlier and subsequent time periods 1968–1973 and 1979–1983. Sharp et al (1996) found no evidence of a significant overall excess of leukaemia or non-Hodgkin lymphoma or of a trend in risk related to Rosyth.

5.7 The true significance of the result for leukaemia and non-Hodgkin lymphoma in the population living near Rosyth is difficult to assess. It should be borne in mind that it is a product of multiple significance testing: this is in contrast to Sellafield, Dounreay, Aldermaston, Burghfield and Harwell, which were all individually selected for investigation in earlier studies. It is also important to note that the magnitude of the possible increase in risk of leukaemia and non-Hodgkin lymphoma in the vicinity of Rosyth is very much smaller than those found in the studies of the sites listed above.

Table 5.1 Results for leukaemia and non-Hodgkin lymphoma in 1969–1993 in 25-km regions around British Energy and Magnox Generation stations in Great Britain

Site (start-up year)	No. wards[†]	Obs	Exp	Obs/Exp (SIR)	Test choice[‡]	p-value[§]
Berkeley (1961)	135	139	137.72	1.009	2	0.666
Bradwell (1961)	105	95	99.21	0.958	1	0.499
Chapelcross (1958)	33	24	29.83	0.805	2	0.732
Dungeness (1965)	37	21	22.80	0.921	2	0.536
Hartlepool (1983)	137	77	77.96	0.988	1	0.193
Heysham (1983)	97	26	32.08	0.810	2	0.907
Hinkley Pointt (1964)	80	67	65.32	1.026	1	0.275
Hunterston (1963)	58	43	50.92	0.844	2	0.741
Oldbury (1967)	150	177	170.19	1.040	1	0.432
Sizewell (1965)	32	11	14.23	0.773	2	0.616
Torness (1988)	11	0	2.33	0.000	2	0.901
Trawsfynydd (1964)	27	5	7.43	0.673	2	0.888
Wylfa (1969)	33	7	11.12	0.629	2	0.908

[†] Excluding wards with zero population under 15 years.
[‡] The tests selected were as follows:
1 Linear Risk Score (LRS) test using 1/(ward distance) as a score,
2 LRS test using the square root of 1/(ward rank) as a score.
[§] p-value using chosen (unconditional) test, based on 10,000 simulations.

Table 5.2 Results for solid tumours in 1969–1993 in 25-km regions around British Energy and Magnox Generation stations in Great Britain

Site (start-up year)	No. wards[†]	Obs	Exp	Obs/Exp (SIR)	Test choice[‡]	p-value[§]
Berkeley (1961)	135	197	212.12	0.929	1	0.966
Bradwell (1961)	105	148	150.71	0.982	1	0.321
Chapelcross (1958)	33	51	48.51	1.050	2	0.527
Dungeness (1965)	37	35	34.83	1.005	2	0.375
Hartlepool (1983)	137	140	130.84	1.070	1	0.110
Heysham (1983)	97	55	60.00	0.917	2	0.640
Hinkley Point (1964)	80	99	101.33	0.977	1	0.671
Hunterston (1963)	58	90	83.22	1.082	2	0.553
Oldbury (1967)	150	252	263.54	0.956	1	0.897
Sizewell (1965)	32	22	24.81	0.887	2	0.689
Torness (1988)	11	2	3.62	0.553	2	0.831
Trawsfynydd (1964)	27	10	12.56	0.796	2	0.761
Wylfa (1969)	33	22	19.01	1.157	2	0.756

[†] Excluding wards with zero population under 15 years.
[‡] The tests selected were as follows:
1 LRS test using 1/(ward distance) as a score,
2 LRS test using the square root of 1/(ward rank) as a score.
[§] p-value using chosen test, based on 10,000 simulations.

Table 5.3 Results for leukaemia and non-Hodgkin lymphoma in 1969–1993 in 25-km regions around nuclear installations other than those in Table 5.1

Site (start-up year)	Operator	No. wards[†]	Obs	Exp	Obs/Exp (SIR)	Test choice[‡]	p-value[§]
Aldermaston (1952)	Atomic Weapons Establishment (AWE)	135	176	157.29	1.119	2	0.182
Amersham (1940)	Amersham plc	316	477	470.24	1.014	2	0.283
Burghfield (1950)	AWE	179	251	229.67	1.093	1	0.023
Capenhurst (1953)	British Nuclear Fuels (BNFL)	228	391	384.23	1.018	1	0.055
Cardiff (1979)	Amersham plc	151	132	129.58	1.019	2	0.247
Chatham (1967)	Ministry of Defence (MOD)	222	325	318.36	1.021	1	0.535
Devonport (1973)	Private (formerly MOD) dockyard	64	66	74.14	0.890	2	0.228
Dounreay (1959)	United Kingdom Atomic Energy Authority (UKAEA)	5	9	3.87	2.324	1	0.014
Faslane (1963)	MOD	42	41	47.72	0.859	2	0.645
Harwell (1946)	UKAEA	111	95	103.19	0.921	2	0.968
Holy Loch (1961)	US Naval Base	40	44	50.95	0.864	2	0.721
Rosyth (1963)	Private (formerly MOD) dockyard	168	218	210.77	1.034	2	0.021
Sellafield (1950)	BNFL and UKAEA	32	25	21.95	1.139	2	0.018
Springfields (1948)	BNFL and UKAEA	184	182	192.12	0.947	1	0.413
Winfrith (1967)	UKAEA	69	62	72.82	0.851	2	0.503

[†] Excluding wards with zero population under 15 years.
[‡] The tests selected were as follows:
1 Linear Risk Score (LRS) test using 1/(ward distance) as a score,
2 LRS test using the square root of 1/(ward rank) as a score.
[§] p-value using chosen (unconditional) test, based on 10,000 simulations.

Sites previously considered in earlier COMARE reports

Sellafield

5.8 Sellafield was the first site for which it had been suggested that radioactive discharges were associated with increased levels of childhood cancer. This hypothesis was examined by the Advisory Group chaired by Sir Douglas Black in 1984 and by COMARE in 1986 with no conclusive evidence of an association being found between discharge levels and childhood cancer incidence. Historically, Sellafield is the UK nuclear site with the largest of all radioactive discharge levels, which peaked in the 1970s and have since declined to the very much lower levels seen at present. We re-examined the original hypothesis, in considerable depth, in our Fourth Report (COMARE, 1996). We examined all the known pathways of exposure to man from both external and internal radiation sources, including sea-to-land transfer. We examined the risks to different stages of human development from the fetus and embryo to the adult and also the risk to different tissues and we incorporated all the variables that could introduce uncertainty in the dose calculations for which data were available. In our Fourth Report we also looked at other possible hypotheses concerning the site and the observed level of childhood cancer: these ranged from an investigation of the non-radioactive chemicals used and discharged from the site, to hypotheses concerning infectious aetiologies for childhood leukaemia. We concluded that the excess of childhood leukaemia and non-Hodgkin lymphoma in the area, which is mainly located in the local

Table 5.4 Results for solid tumours in 1969–1993 in 25-km regions around nuclear installations other than those in Table 5.2

Site (start-up year)	Operator	No. wards[†]	Obs	Exp	Obs/Exp (SIR)	Test choice[‡]	p-value[§]
Aldermaston (1952)	Atomic Weapons Establishment (AWE)	135	278	239.27	1.162	2	0.003
Amersham (1940)	Amersham plc	316	717	718.73	0.998	2	0.559
Burghfield (1950)	AWE	179	398	347.92	1.144	1	0.011
Capenhurst (1953)	British Nuclear Fuels (BNFL)	228	654	665.17	0.983	1	0.941
Cardiff (1979)	Amersham plc	151	222	227.43	0.976	2	0.756
Chatham (1967)	Ministry of Defence (MOD)	222	466	486.67	0.958	1	0.833
Devonport (1973)	Private (formerly MOD) dockyard	64	121	112.34	1.077	2	0.572
Dounreay (1959)	United Kingdom Atomic Energy Authority (UKAEA)	5	3	6.29	0.477	3	0.868
Faslane (1963)	MOD	42	71	77.88	0.912	2	0.929
Harwell (1946)	UKAEA	111	188	156.19	1.204	2	0.003
Holy Loch (1961)	US Naval Base	40	75	83.06	0.903	2	0.834
Rosyth (1963)	Private (formerly MOD) dockyard	168	392	343.31	1.142	2	0.016
Sellafield (1950)	BNFL and UKAEA	32	40	35.96	1.112	2	0.177
Springfields (1948)	BNFL and UKAEA	184	348	327.82	1.062	1	0.245
Winfrith (1967)	UKAEA	69	113	111.55	1.013	2	0.782

[†] Excluding wards with zero population under 15 years.
[‡] The tests selected were as follows:
1 LRS test using 1/(ward distance) as a score,
2 LRS test using the square root of 1/(ward rank) as a score,
3 Poisson maximum test.
[§] p-value using chosen (unconditional) test, based on 10,000 simulations.

village of Seascale, when examined in the context of the national distribution of these diseases, is highly unusual in that it has persisted for some tens of years and that it is unlikely to be due to chance. However, we found that no one factor could account for the observed increase in the level of disease, although infection, at least in part, could not be ruled out as having some causal association (see paragraph 2A.10). Some interaction between different factors could also not be ruled out.

Dounreay

5.9 During its enquiry concerning the area around Sellafield, the Advisory Group chaired by Sir Douglas Black had requested information about the incidence of childhood leukaemia around Dounreay, the only other nuclear installation in the UK where nuclear fuel reprocessing was carried out. At that time the data did not suggest any evidence of an increase in leukaemia around this site. However, a further analysis (Heasman et al, 1986b), prompted by the public enquiry into a new reprocessing site, suggested an elevated incidence of leukaemia in young people in the local town of Thurso. COMARE was asked to investigate and report, which we did in our Second Report (COMARE, 1988). We identified six cases of leukaemia among people aged up to 25 years living within 25 km from Dounreay during the period 1968–1984. We

examined the radioactive discharges from the site and commented on the considerably lower levels of discharges from Dounreay than from Sellafield. We also noted that there was no excess of other types of childhood cancer in the area. We had to re-examine some of our conclusions on the possible health effects from radioactivity released from the Dounreay site when radioactive particles were found on the Dounreay foreshore (COMARE/RWMAC, 1995) and on a local beach, Sandside Bay (COMARE, 1999). Although highly critical of parts of the nuclear industry and its regulators concerning how this information came to light, we could still find no causal link between levels of radioactivity in the general environment and that of childhood cancer in the local area. A further study (Roger Black, personal communication) showed that, although there was an increased level of childhood leukaemia in this area in the years 1968–1996, this increase did not achieve statistical significance, as no cases had occurred since 1992: hence the excess seen in the 1980s has not persisted over decades as it has in the case of Sellafield.

Aldermaston, Burghfield and Harwell

5.10 The leukaemia incidence in young people living in the areas around these sites was studied because clinicians at the Royal Berkshire Hospital, Reading, suspected that more cases of childhood leukaemia were being referred to the hospital than would normally have been expected. Although the incidence was relatively low compared to that at Seascale or the area around Dounreay, the area is much more densely populated and therefore larger numbers of cases were registered. The topic was the subject of a Yorkshire Television programme entitled *Inside Britain's Bomb* broadcast in December 1985. A study by Roman et al (1987) found that there was a statistically significantly increased incidence of childhood leukaemia in an area within 10 km of either Aldermaston or Burghfield in the years 1972–1985. This increase was found only in the age group 0–4 years. These studies were referred to COMARE for advice. We also had access to registration data from the Childhood Cancer Research Group (CCRG) in Oxford. These data showed that for the years 1971–1982, there was also an excess of all childhood cancers, other than leukaemia, in the same area and in the same age group (0–4 years) as that found by Roman et al.

5.11 COMARE's Third Report identified a significant excess of childhood leukaemia cases confined to those aged 0–4 years, among whom 29 cases were observed resident less than 10 km from Aldermaston or Burghfield against 14.4 expected (COMARE, 1989). There were also 30 cases of other cancer in this age group and area compared to 19.4 expected. We concluded that although there is a small but significant excess of childhood leukaemia and other cancers in the vicinity of these establishments, the radioactive discharges from these and the Harwell site were far too low to account for the epidemiological findings.

5.12 The situation concerning these three sites is complicated because of their close proximity to each other. In fact, 25-km circles drawn around each site all overlap. The discharges from Aldermaston have historically been much greater than those from Burghfield; thus if the excess around Burghfield were due to radioactive discharges one would presumably expect greater excess around Aldermaston than that observed. However, it has been argued that the liquid discharge point from Aldermaston is closer to Burghfield. To put the levels of discharge in further perspective it should be pointed out that at peak levels the Sellafield discharges were over 200,000 times greater than the Aldermaston and Burghfield discharges combined. Furthermore, we noted that the radioactive discharges from Aldermaston and Burghfield were only half the level of the radioactive discharges from the nearby coal-fired power station at Didcot. The Didcot discharges also contain a significant proportion of alpha emitters such as radium and polonium-210. We discussed all of these complexities in detail in our Third Report: nevertheless, we noted that the rate

around Aldermaston, in an analysis based on rates within 10-km circles around the sites, was raised, albeit without statistical significance. The new statistical analyses do not indicate any tendency for an increased rate closer to these sites within the 25-km circles, although the fact that these circles all overlap makes interpretation complex. However, it is possible that the significant effects are a reflection of the raised rates in Berkshire and south Oxfordshire generally.

Overall distribution of childhood cancer in Great Britain

5.13 In considering all of these results, we need to do so in the light of the distribution of childhood cancer in Britain. This distribution has been considered in detail in previous chapters of this report, but two points generally relevant to nuclear sites need to be made here. First, rates of childhood cancer differ from one part of the country to another and these differences are unlikely to be due to differing extents of cancer registration. They reflect environmental, genetic or social and behavioural differences that are not yet understood.

5.14 A second general point concerns clustering. Both leukaemia/non-Hodgkin lymphoma and some solid tumours appear to occur in clusters at rates above those that would occur by chance. Population mixing seems to be associated with some of these, but the underlying biological mechanism of population mixing remains obscure: some authors have speculated that variations in exposure to infections may be involved. While plausible in principle, more definite evidence as to the role of infection is needed before this can be properly evaluated. Statistical analysis of the times and places of occurrence of cases cannot by itself tell us whether any particular cluster is a chance event or not. However, for sites where observed rates are considerably higher than expected, the excess might be attributable to causative factors that result in clustering. In our Tenth Report we expressed our opinion that the excesses around Sellafield and Dounreay are unlikely to be due to chance, although there is not at present a convincing explanation for them (COMARE Second and Fourth Reports). In the light of this opinion we feel further study of these two sites might be warranted and this will be reflected in the recommendations of this report.

CHAPTER 6

DISCUSSION: RESULTS OF NEW ANALYSES AND THEIR RELEVANCE TO THE SEARCH FOR POSSIBLE CAUSATIVE FACTORS IN CHILDHOOD LEUKAEMIA AND OTHER CHILDHOOD CANCERS

Introduction

6.1 In Chapters 3 and 4 of this report we have presented a series of analyses related to the geographical epidemiology of childhood cancer and have discussed their relevance to general questions concerning the aetiology of these diseases. In Chapter 5 we summarise our previous report, the Tenth COMARE Report, on the occurrence of childhood cancer around nuclear installations and, in paragraphs 5.13 and 5.14, relate these to our current findings. In this chapter we discuss both the geographical analyses generally and their relation to the nuclear installation studies.

Some geographical and socio-demographic factors affecting the incidence of childhood cancers (Chapter 3)

6.2 There are two major publications on international variations in rates of childhood cancer (Parkin et al, 1988, 1998) and a number of papers on variations in rates for specific tumours, but few data are available on variations within countries. No major factor in the environment involving a potential carcinogen affecting the incidence of childhood cancer within the UK has been unequivocally identified. In Chapter 3 we have considered the possible effects of some socio-demographic factors, particularly socio-economic status. The results provide strong evidence that the incidence rates of some forms of childhood cancer are related to region within a country and to socio-demographic factors such as socio-economic status and population density. There is a strong relationship between rates for leukaemia and socio-economic status, areas of high socio-economic status having higher rates of leukaemia. This, of course, is in contrast to most childhood illnesses where lower socio-economic status is associated with higher incidence rates. This effect appears to be stronger when acute lymphoblastic leukaemia, the most common form of leukaemia in children, is considered alone rather than analysing all leukaemias together. The socio-economic-status effect also applies to some other diagnostic groups, including the second most common form of childhood cancer, brain and spinal tumours. However, for this group the association with population density is about as strong as that for socio-economic status, though the effect of either is considerably reduced when allowance is made for the other. Socio-economic status and/or population density may also be similarly related to factors affecting incidence rates for some other childhood cancers. In contrast to these findings, Hodgkin lymphoma at ages 0–9 years is found to be more common in areas of *low* socio-economic status and is very strongly associated with overcrowding; this is consistent with previous findings and with the possible viral aetiology of the mixed cellularity form of this disease, the predominant form in this younger age group. There are, in addition, strong regional effects on the registration rates of some childhood cancers. One obvious explanation of such effects is that they are artefacts caused by differing ascertainment levels in the different regions and do not reflect true variation in incidence. The high overall ascertainment for childhood tumours, however, and the fact that the regions with the highest registration rates differ for the

different tumour groups, argue against this explanation. Similarly, it might be argued that the association between higher incidence and high socio-economic status is due to better diagnosis in more affluent areas.

6.3 From the regression analyses it appears that the regional and socio-economic-status effects are, at least to some extent, independent, ie neither can be explained by the other, though each may of course be some approximate measure of a real underlying aetiological factor. A possible explanation of the variations in incidence rates for childhood leukaemia is that the rates are affected by 'population mixing' (see Chapter 2). This is discussed, and new results presented, in Chapter 3, Annex 3A. This annex summarises a paper in which childhood leukaemia rates are analysed in relation to various measures of population mixing and socio-demographic variables. The authors measured population mixing by 'diversity of incomers' – a measure, derived from census data for each ward, of the number of immediately previous wards of residence of people who had moved into that ward during the year before the census. The main finding from this study in relation to population mixing is that rates of acute lymphoblastic leukaemia for children aged 1–4 years tend to be higher where this measure of diversity of incomers is high. This finding is consistent with Kinlen's hypothesis concerning exposure to infection (Chapter 2).

Statistical problems in the interpretation of the results of Chapter 3

6.4 Two general remarks are necessary concerning the interpretation of the analyses in Chapter 3. First, in carrying out multiple statistical tests it is inevitable that a number of 'false positives' will occur. The point here is that the question of whether an observed effect is likely to reflect a causal mechanism rather than being due to chance is assessed on the basis of statistical significance tests: the probability of results as extreme as those observed occurring if there is really no association between the factors being investigated – for instance, socio-economic status and leukaemia incidence – is calculated. Probabilities that are sufficiently low are 'statistically significant'. However, if a large number of such tests is carried out the analysis ought to be adjusted to give probabilities that allow for this; without such adjustment results that are 'formally' significant may simply reflect the fact that in a large number of analyses some extreme, and apparently meaningful, results can be expected to occur by chance. Here, as is frequently the case, there is no obvious way of making the necessary adjustment. Thus in interpreting the present results we have attempted to take into account not only the results of formal significance tests but also the patterns of results and their relation to previously published studies. Second, the results in Chapter 3 are based on 'ecological' analyses, ie they relate to population groups rather than to individuals. It is well known that the results of such analyses may be misleading, in that the associations observed may not hold at the individual level ('the ecological fallacy'). Against this, it is of course possible that the aetiologically relevant factors are those relating to areas rather than to individuals. In fact, the results reported here appear to be largely consistent with those from other types of study.

Clusters and clustering (Chapter 4)

6.5 Public and media concern about childhood cancer around nuclear installations has usually focused on reports of 'clusters' rather than on analyses reporting high incidence rates. Such reports are not usually based on systematic analyses but reflect a perception that an unusual pattern of occurrence has been identified. Such perception may well be correct, but the way in which most clusters come to notice does not permit any formal analysis of their validity to be made. In Chapter 4 we have presented the results of a series of systematic analyses directed towards the question of whether either spatial or space–time clustering is a general phenomenon. The questions addressed by these analyses are, first, whether cases tend to be concentrated in certain areas ('spatial' clustering) and, second, whether there are areas which for limited time periods

show an increased incidence ('space–time' clustering). The analyses of spatial clustering showed statistically significant evidence of weak clustering for acute lymphoblastic leukaemia (ALL) over the whole age range 0–14 years and the childhood peak (1–4 years) but not for 5–14 years. There was also significant clustering for the age range 0–14 years for the group 'leukaemia and lymphoma', renal tumours, soft-tissue sarcomas, for all cancers combined and for the group consisting of 'all cancers except leukaemia and lymphoma'. These results suggest a greater commonality of aetiological factors among different childhood cancers than had been previously suspected The analyses of space–time clustering showed statistically significant evidence of clustering for acute lymphoblastic leukaemia at ages 1–4 years and over the whole age range 0–14 years but not for 5–14 years; there was also significant space–time clustering at ages 0–14 years for soft-tissue sarcomas and osteosarcoma. For central nervous system (CNS) tumours, the most common childhood cancer after leukaemia, neither type of clustering showed positive results.

What do clusters mean?

6.6 When analyses suggest that any possible clustering in a particular area is not statistically significant, ie is just due to chance, it means that the various factors (genetic, environmental, etc) that lead to cancer are randomly distributed around the area, or alternatively are distributed sufficiently homogeneously that the analyses do not have the statistical power to detect any non-randomness. When analyses indicate that more clustering exists than can easily be accounted for by chance, it suggests that one or more risk factors are concentrated in particular areas (and, in the case of space–time clustering, for particular periods of time). There are known examples of clusters that could reflect such a situation – eg Seascale or Fallon, Illinois, USA (Steinmaus et al, 2004) – but the factors involved are still unknown.

Interpretation of results concerning clustering in this report

6.7 The analyses reported here do not address the question of what aetiological factors are responsible for the clustering or where the clusters are. The main conclusions are consistent with those of Chapter 3; in particular, the observed spatial clustering may reflect the effects of the same socio-demographic factors as those analysed in that chapter, and this may be in some way related to patterns of infection. This latter possibility, particularly in relation to childhood leukaemia, has been the subject of much research (see Chapter 2). We emphasise again that it is not suggested that leukaemia or other childhood cancers can be spread from one child to another. Both spatial and space–time clustering could of course result from other factors that vary in space and/or time. The types of analysis carried out in Chapter 4 are not designed to identify the location of clusters, and we have not attempted such identification for this report. The results of analyses summarised in Chapter 5 suggest that there is no general clustering around nuclear installations.

The Seascale cluster

6.8 Although, as we have explained, there is no evidence for clustering around nuclear installations in general, there is good evidence that there is an excess of cases among children in Seascale, the nearest village to the Sellafield reprocessing plant (see paragraph 5.8). There were 21 cases of cancer in young people who were born or diagnosed in Seascale between 1954 and 2001 (see Table 2.2 of our Seventh Report). Seven of these were acute lymphoblastic leukaemia which in the present study has shown both 'spatial' and 'space–time' clustering. There were two CNS tumours, a group that showed no evidence of any form of clustering in the present study. The result with acute lymphoblastic leukaemia is consistent with the proposition that at least part of the Seascale excess can be attributed to risk factors which are widespread in the country and which tend to show some degree of clustering in general. The findings relating to cancers other than leukaemia are consistent with the results presented in Chapter 4 of the present report where, nationally, spatial clustering was found

for 'all cancers combined'. As discussed in our Fourth and Seventh Reports, there is no generally accepted explanation for the increased incidence of childhood cancer in Seascale. It seems unlikely to be simply attributable to radioactive discharges, and it was suggested that, for leukaemia, it may be largely or wholly due to the effects of population mixing (cf. paragraph 2A.10). The results of the present study would not be inconsistent with such an interpretation, since, as we have commented in Chapter 4, there may be some commonality of aetiology between childhood ALL and other childhood cancers.

Nuclear installations (Chapter 5)

6.9 Published studies concerning nuclear installations in the UK are reviewed in Chapter 5; the overall conclusion from these studies and those from other countries (Canada, France, Germany, the USA) is that there is no general increase in either adult or childhood cancer or leukaemia rates around nuclear installations. Some statistically significant results have been reported (Sellafield, Dounreay, Aldermaston/Burghfield, Cap de la Hague in France, and the Krümmel plant in Germany) but there is no consistent pattern of results and, with the exception of Seascale and Dounreay, no evidence that the increased rate continues over time. Much of the public and media concern about the possibility of increased cancer rates around nuclear installations, and many of the scientific publications, relate to childhood leukaemia. In our Tenth Report, and briefly in Chapter 5, we have described the results of a series of updated analyses concerning the incidence of childhood leukaemia and other cancers in the vicinity of nuclear sites in England, Scotland and Wales. These analyses are new: they use new and extensive data and are based on carefully defined start-up dates for each installation. In addition, for each site, a series of computations was carried out to determine the most appropriate statistical test of the hypothesis that childhood leukaemia or cancer rates were increased in the vicinity of that site. The conclusion from these analyses, as with previous studies, is that there is no evidence of a general increase in childhood leukaemia or cancer rates around nuclear power generating plants. Some statistically significant results are found in these new analyses for certain other nuclear installations (Sellafield, Dounreay, Aldermaston/Burghfield/Harwell and Rosyth); these are largely in line with previous findings. It has been suggested that higher rates in the vicinity of some nuclear installations might be explained by there being an increased risk in the children of workers occupationally exposed to radiation (Gardner et al, 1990). This hypothesis was considered in great detail in the COMARE Seventh Report and the committee concluded that this explanation was unlikely.

Geographical variations in relation to nuclear installations

6.10 One of our main concerns in this report, and the earlier recommendations leading to it, is the question of whether reports of an increase in the incidence of childhood leukaemia or other cancers around certain nuclear installations can be explained in terms of the general variations in incidence analysed in Chapter 3 or the patterns of clustering analysed in Chapter 4. Ionising radiation in sufficient doses can cause childhood cancers; the analyses discussed in this report do not, however, support the suggestion that radiation emitted from nuclear installations is implicated. Some of the findings concerning nuclear installations reported previously may be explained by the generally higher rates in the regions in which they are situated. Others, particularly Sellafield and Dounreay, may, as suggested by Kinlen (1995), be a consequence of high levels of population mixing in the vicinity – which, in turn, is thought to be related to patterns of exposure to infections (see Chapter 2 and Chapter 3, Annex 3A). The analyses in Chapter 3 suggesting that the incidence of both leukaemia and some other cancers may be related to socio-economic status (and hence to differences in the likelihood of early exposure to infection) also support this explanation, although there could, of course, be other aetiological factors related to socio-economic status.

Relevance of the findings to the search for possible causative factors in childhood cancer

6.11 Very little is known about causative factors in childhood cancer. The analyses in Chapters 3 and 4 are potentially relevant to various other hypotheses about causative factors, insofar as such factors may vary geographically or temporally. (See Chapter 2.) Inferences of the type described in Chapter 3, based on geographical analyses, will generally be less satisfactory than those based on individual records, simply because what is true of an area is not necessarily true of individuals within it. On the other hand, some causative factors may be related to characteristics of the area rather than to those of a particular individual. (See also paragraph 6.4.)

6.12 The finding that incidence rates for a number of diagnostic groups are higher among children in areas of higher socio-economic status has many possible explanations. The suggestion that for childhood leukaemia early exposure to infection (which may reasonably be assumed to be associated with lower socio-economic status) may affect the immune system in such a way as to decrease the likelihood of childhood leukaemia occurring subsequently is widely accepted. On the basis of the results reported here, we speculate that such a mechanism may apply also to other childhood cancers.

6.13 A number of other factors that vary geographically have also been suggested as possible causes of childhood cancer. These factors include ultraviolet radiation, radon and gamma radiation, electromagnetic fields, pesticides, traffic, exhaust fumes and other sources of pollution. Hypotheses about these factors can be tested using either data on individuals (obtained, for example, from interviews or medical records) or from geographical analyses of the type described in Chapter 3. The analyses reported in Chapter 3 do not directly address any of these questions but, to the extent that any of the postulated causative factors are related to the factors analysed here, these analyses may be relevant.

CHAPTER 7

CONCLUSIONS

Introduction

7.1 This, our Eleventh Report, has been produced in response to Recommendations 4 and 5 of our Third Report (COMARE, 1989). Recommendation 4 stated that 'studies of the geographical distribution of childhood cancer incidence on a nation-wide basis be carried out … thus enabling the patterns found around nuclear sites to be seen in the context of patterns in the rest of the UK'. Recommendation 5 of the Third Report went on to say that 'once the results of the studies outlined in Recommendation 4 are available, this Committee should be asked to participate in a review of the evidence relating to the incidence of childhood cancer around nuclear installations'. Our purpose, therefore, was two-fold, but primarily in this report we respond to the recommendation for a study of the nature of the geographical distribution of all childhood cancers in England, Wales and Scotland. Having done this we have considered the distribution of these cancers around all the main nuclear installations in Great Britain and placed these findings in the context of the distribution as seen in Great Britain as a whole. This second objective was considered in detail and published as our Tenth Report (COMARE, 2005) so is not covered to the same depth here. The studies described in our Tenth Report are mainly in response to our own conclusion in our Third Report 'that it was unlikely that useful information would emerge from further detailed investigations of alleged increased childhood cancer incidence around individual nuclear installations'. However, we have in fact been asked to investigate several claims of excess childhood cancer around specific individual nuclear installations since the publication of our Third Report. The results of these individual studies, and the distribution of childhood cancer around nuclear installations in Great Britain, considered in our Tenth Report, can all be found on our website, www.comare.org.uk.

7.2 To carry out the studies as we proposed in our Third Report required a very large database compiled over a considerable time scale. The database we used was constructed from the National Registry of Childhood Tumours by staff of the Childhood Cancer Research Group in Oxford. The current studies were based on analyses of a dataset consisting of 12,415 cases of childhood leukaemia and non-Hodgkin lymphoma (NHL) and 19,908 cases of children with solid tumours registered under the age of 15 years in England, Wales and Scotland from 1969 to 1993 inclusive. We believe this is the largest dataset of childhood cancer cases ever compiled and analysed. Because of the size of the database analysed, we can be much more confident in the results of these statistical analyses than in the findings of the very much smaller studies carried out previously.

7.3 This report relies on the use of a variety of very specific statistical techniques with which the general reader may not be familiar and which required careful consideration. The report contains very large numbers of analyses, which have not been published previously. To make this report easier to read, additional data and results of the analyses have been made available on the CCRG website, www.ccrg.ox.ac.uk/COMARE11.

Aetiological factors in childhood cancer: review of existing information

7.4 The causes of the vast majority of childhood cancers are unknown. Certain inherited syndromes, which occur at very low frequencies in the general population have been shown to be associated with cancers in childhood, the commonest being an increase in the risk of the development of leukaemia as a rare consequence of Down syndrome. There is also good evidence that certain types of childhood Hodgkin lymphoma are linked to exposures to the Epstein-Barr virus.

7.5 That aside, virtually all childhood cancers, including acute lymphoblastic leukaemia and central nervous system (CNS) tumours – the two largest groups of childhood cancer, have unknown causes. Since the late 1980s, much attention has been focused on three hypotheses regarding the possible aetiology of childhood leukaemia. These are the effect of population mixing, the possible involvement of infectious agents, and the possible effect of immature immune competence due to reduced exposure to common infections in the first year of life. Consideration has also been given to the minimal contribution of specific potential causative agents including non-ionising radiation, radon gas, nuclear power sources and a variety of natural and man-made chemicals found in the general environment. Much of the work of this committee has been concerned with a consideration of all of these potential causative agents.

7.6 It is possible that other environmental sources of risks exist, but currently there is little evidence of any association with cases of childhood cancer. These risks are small, but there is also a lack of biological models for how these environmental agents react with living tissue. Studies of genetic susceptibility with or without environmental triggers have not produced any clear causal associations with the vast majority of cases of the most common form of childhood leukaemia. Furthermore, it is not possible to rule out the fact that several factors might be involved in the pathways which might lead to childhood cancer, as it is most likely that more than one pathogenic step is required to create a childhood neoplasm. Indeed this is the current consensus position in the medical and scientific communities.

Childhood cancer rates analyses at country, counties, district and ward levels

7.7 At each geographical level, from the whole country to the electoral ward, each cancer type displays variation in rates, which are thought not to be random.

7.8 When socio-economic status, at district and ward level, is analysed along with the incidence data, many childhood cancer rates including leukaemia have been shown to be slightly higher in affluent areas compared to more deprived areas. The reason for this is not known, although it is tempting to link leukaemia with the infectious agent hypotheses mentioned earlier. The present study shows that childhood cancer rates other than childhood leukaemia are also slightly higher in areas of high socio-economic status. These other childhood cancers have not been linked to population mixing, infectious agents or immune incompetence. So these hypotheses may or may not be relevant to this finding. The social class association for childhood leukaemia has been known for some time. The fact that this also appears to apply for other childhood cancers is new and as far as we know unique to this study.

Spatial and space–time clustering

7.9 In Chapter 4 of this report we have addressed the questions as to whether or not the various childhood cancers have a ‘natural’ tendency to aggregate closer in space (spatial clustering) or closer in both time and space (space–time clustering) than one would expect by chance alone. These are studies of the phenomenon of clustering, not of individual clusters.

7.10 The ‘space only’ method used shows that, over the 25-year period, there is some good evidence for weak case aggregation of acute lymphoblastic leukaemia, some other childhood cancers and all cancer aggregated. The term weak is used because the average numbers of cases in each ward is low, but the results reinforce the concepts introduced in Chapter 3 that case occurrence is not entirely random.

7.11 In a different way the space–time clustering analysis has attempted to resolve issues at even smaller areas of geographical resolution (cases occurring within a few years and a few kilometres of each other). This method also shows (like spatial clustering) clustering for acute lymphoblastic leukaemia as well as for some other solid tumours of childhood.

7.12 When the results of the two methods are compared, there is some agreement in that both methods highlight acute lymphoblastic leukaemia as exhibiting clustering. The results from other cancers are mixed. For example, there is no agreement about Hodgkin lymphoma or CNS tumours. However, the clustering of soft-tissue sarcomas and bone tumours show some agreement between the two methods. The results for tumours other than leukaemia are new and need independent confirmation.

Studies of cancer made around nuclear installations

7.13 There is no evidence for unusual aggregations of childhood cancer cases in populations living near nuclear power generation plants in Great Britain. There are excesses of cases of some types of childhood cancer in the areas near to the Sellafield, Dounreay, Aldermaston, Burghfield and Harwell nuclear installations (because of their close proximity the latter three installations have been discussed together). However, the results for all these sites were previously known. Furthermore, there is no consistency regarding either the type of nuclear activity at each site, the time span involved, or the nature of the excess cases involved. We recommend reference to our Tenth Report for a detailed examination of this topic. In summary, our analyses demonstrated similar findings to those in previous studies, such as the excess of childhood cancer in the village of Seascale near Sellafield and the excess of childhood leukaemia in the area around Dounreay. However, we have pointed out the anomalies between some of these studies such as the longevity of the excess of both childhood leukaemia and other childhood cancers in Seascale and the possibly transient excess of childhood leukaemia but not other childhood cancers around Dounreay. The known excess around Aldermaston, Burghfield and Harwell has been discussed in terms of the lower doses received by the general public from radioactive discharges from those sites than from the radioactive discharges from the local coal-fired power station at Didcot. These excesses are also discussed in terms of the general incidence of childhood cancer in Berkshire and south Oxfordshire.

7.14 Among nuclear installations other than power generating stations, only one finding differs from previously published results. Although the overall incidence of leukaemia and non-Hodgkin lymphoma in children living within 25 km of Rosyth was close to the expected value (relative risk, RR = 1.03), there was evidence of a trend in risk with distance from the plant. This latter aspect of our findings differs from previously published work using similar but not identical methods. Because of this, it is not possible to conclude that living near the site at Rosyth confers a genuinely higher risk of leukaemia or non-Hodgkin lymphoma. It is clearly of importance to establish the reasons for the differences between the two sets of results: therefore the committee has recommended that the research workers concerned undertake a detailed comparison of the data and methodologies used. This process is already under way.

Main conclusions

7.15 The major caveats about these analyses are related to the effects of multiple statistical testing because this can result in spuriously high apparent levels of association. In layman's terms this means that the more comparisons that are made in an analysis, then the more likely it is that – purely by chance – results are obtained that appear to be statistically significant. That having been said, very large studies, with detailed analyses, are required to investigate the geographical distribution of rare diseases. This report deals with the largest dataset of childhood cancer ever examined.

7.16 In this report, childhood cancers of many types have been shown not to occur in a random fashion at country, county, county district and ward levels. Furthermore, this non-random distribution is seen (albeit more weakly) at very local levels as defined by distributions within wards or within short time periods (under five years) and very close (under 5 km). This latter distribution is referred to as a tendency towards 'clustering'. We wish to emphasise that this 'clustering effect' is weak (ie based on small numbers in census wards).

7.17 By contrast, the search for increased risk levels near to nuclear power generation sites (by the use of other methods) shows no pattern of excess cases of childhood cancer close to the sites of these types of nuclear installation. Our analyses confirmed the excesses in areas close to the Sellafield, Dounreay, and Aldermaston, Burghfield and Harwell sites, which were already known. There is, therefore, little support for the hypothesis claiming that there is a link to radioactive discharges as a general cause of childhood cancer in Great Britain. It is possible that at least one or two of the three unusual aggregations around nuclear installations could be a result of the more general non-random case distribution we have described. This is less likely with the excess in the village of Seascale near Sellafield due to the prolonged nature of the case occurrence and its range of cancers. At both Sellafield and Dounreay, population mixing has been put forward by some authors as a possible explanation for the cases of childhood leukaemia occurring nearby.

7.18 Although the geographical distribution of childhood cancers is non-random, the reasons for this are unknown. Much attention has been given to infection/immune system based hypotheses almost to the exclusion of other possible explanations, which include other environmental agents such as sources of pollution as well as aspects of genetic susceptibility. All of these hypotheses require further research.

7.19 We have noted that the development of childhood cancer is a multi-step process, and the current consensus is that two or more alterations to the genetic code of a previously normal cellular population are most likely required before malignant disease is manifest. The results of the current study are consistent with an infective process (including immature immune competence) being associated with at least one of these steps. This does not mean that childhood cancer can be passed from child to child in the usual manner of infectious illnesses. It implies that it is possible that one of the steps on the way to the development of a childhood cancer is a rare and unusual response to one or more infective agents. However, the results are also consistent with a hypothesis that the non-random distributions could be due to heterogeneous distribution of other carcinogenic risk factors. It is also possible that such processes may be at work at different steps of the carcinogenic progression and that they may also interact with each other. Further work should be able to address these hypotheses.

CHAPTER 8

RECOMMENDATIONS

In this report we have confirmed that childhood leukaemia occurs in a non-random pattern and in a particular socio-economic distribution. However, we have also made some new and interesting findings principally about the nature of the occurrence of childhood cancers other than childhood leukaemia. In this report many types of childhood cancers have been shown to occur in a non-random fashion at all levels and with similar socio-economic distributions to that shown by childhood leukaemia. We have discussed these new findings in terms of possible aetiologies and, as requested, examined the distribution of childhood cancer around nuclear installation in the UK, where we found no general pattern of increase of these childhood diseases.

Recommendation 1

Understandably, given the complex techniques involved, the methodologies used in the studies covered by this report will come under scrutiny and discussion by the scientific community and there may be different opinions as to whether the most appropriate statistical tests have always been used. We wish to recommend, therefore, that it is important that these new findings are confirmed by independent research, using either different datasets that do not overlap those used in this report or data from other countries. We recommend that research is undertaken into the statistical methodologies used in the study of disease clustering as well as into the examination of the pattern of distribution of these childhood diseases.

Recommendation 2

However, before further studies are carried out in the UK, we recommend that the database held by the National Registry of Childhood Tumours, whose data to 1993 was used in our studies and which currently extends to the end of 2002, be updated and validated to as recent a date as possible. This would allow new data to be used to compare and expand on the findings in this report. It would also allow the use of the most recent census data in any new studies and we consider this important given the socio-economic changes that have taken place in the UK in the 40 years for which cancer registration data are available.

Recommendation 3

Although our new findings need to be confirmed, they do suggest other areas of research that we wish to make the subject of our recommendations. The first of these is the apparent clustering of soft-tissue sarcoma and bone tumours. This finding should be investigated by other agencies and consideration given to the possible aetiological implications and whether or not clustering also occurs in older age groups.

Recommendation 4

We would like to encourage further basic research into the underlying changes that take place at the cellular level that result in carcinogenic changes. Specifically we recommend research into the genetic risk factors in carcinogenesis and leukaemogenesis particularly as they relate to childhood disease.

Recommendation 5

In our Fourth Report (COMARE, 1996: Recommendation 2, page 135) we recommended that the incidence of childhood leukaemia and other cancers in the vicinity of Sellafield should be kept under surveillance and periodic review.

This recommendation was made because we were aware of the public concern about the continuing excess of these diseases in the village of Seascale. We recommend that it is now time for such a review to be undertaken and we reiterate Recommendation 2 of our Fourth Report. It would also be of interest to see if cancer excess now occurs in age groups older than 25 years of age. We recognise that particular technical difficulties will occur dealing with older age groups, partly related to the processes of cancer registrations and to migration. Despite these difficulties, consideration should be given as to whether or not the cancer experience of cohorts of people who have lived or continue to live in Seascale could be brought up to date to answer such questions. Furthermore, given the opinion in our Tenth Report (COMARE, 2005: paragraph 3.13, page 29) that the Sellafield and Dounreay excesses are unlikely to be due to chance, we recommend that such surveillance and review processes are also carried out in the area surrounding Dounreay, where similar public concerns still exist.

Recommendation 6

Finally, we hold serious concerns about possible changes to the way data relating to cancer incidence may be obtained and investigated. Changes already proposed could mean that patients would have the right not to have their data placed on the cancer registry, or that the use of new sources of information to build the cancer registry dataset may remove data items, such as postcodes, which may be vital to the type of research described in this report. In our Seventh Report (COMARE, 2002: Recommendation 5, page 53) we recommended that Government examined any proposed changes in detail so as to ensure that epidemiological studies similar to that described here would not be compromised in the future. We are sad that just four years after publishing this recommendation we have to re-iterate it in this report.

REFERENCES

Ahlbom A, Day N, Feychting M, Roman E, Skinner J, Dockerty J, Linet M, McBride M, Michaelis J, Olsen J H, Tynes T and Verkasalo P K (2000). A pooled analysis of magnetic fields and childhood leukaemia. *Br J Cancer,* **83,** 692–8.

Alexander F E (1993). Viruses, clusters and clustering of childhood leukaemia – a new perspective? *Eur J Cancer*, **29A**, 1424–43.

Alexander F E (1997). Is mycoplasma pneumonia associated with childhood acute lymphoblastic leukaemia? *Cancer Causes Control*, **8**, 803–11.

Alexander F E and Boyle P, eds (1996). *Methods for Investigating the Localized Clustering of Disease*. IARC Scientific Publication No. 135. International Agency for Research on Cancer, Lyon.

Alexander F E, Ricketts T J, McKinney P A and Cartwright R A (1990). Community lifestyle characteristics and risk of acute lymphoblastic leukaemia in children. *Lancet*, **336**, 1461–5.

Alexander F E, Boyle P, Carli P-M, Coebergh J W, Draper G J, Ekbom A, Levi F, McKinney P A, McWhirter W, Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plisko I, Pukkala E, Rahu M, Storm H H, Terracini B, Vatten L and Wray N (1998). Spatial clustering of childhood leukaemia, summary results from the EUROCLUS project. *Br J Cancer*, **77**, 818–24.

Alexander F E, Lawrence D J, Freeland J, Krajewski A S, Angus B, Taylor G M and Jarrett R F (2003). An epidemiologic study of index and family infectious mononucleosis and adult Hodgkin disease (HD): evidence for a specific association with EBV+ve HD in young adults. *Int J Cancer*, **107**, 298–302.

Auvinen A, Hakulinen T and Groves F (2000). Haemophilus influenzae type B vaccination and risk of childhood leukaemia in a vaccine trial in Finland. *Br J Cancer*, **83**, 956–8.

Baldwin R T and Preston-Martin S (2004). Epidemiology of brain tumors in childhood – a review. *Toxicol Appl Pharmacol*, **199**, 118–131.

Balta G, Yuksek N, Ozyurek E, Ertem U, Hicsonmez G, Altay C and Gurgey A (2003). Characterization of MTHFR, GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes in childhood acute leukemia. *Am J Hematol*, **73**, 154–60.

Baron J A (1984). Cancer mortality in small areas around nuclear facilities in England and Wales. *Br J Cancer*, **50**, 815–24.

Barton C J, Roman E, Ryder H M and Watson A (1985). Childhood leukaemia in West Berkshire. *Lancet*, **2**, 1248–9.

Beral V, Newton R and Sitas F (1999). Human herpesvirus 8 and cancer. *J Natl Cancer Inst*, **91,** 1440–41.

Birch J M, Alexander F E, Blair V, Eden O B, Taylor G M and McNally R J Q (2000). Space–time clustering patterns in childhood leukaemia support a role for infections. *Br J Cancer*, **82**, 1571–6.

Bithell J F, Dutton S J, Draper G J and Neary N M (1994). Distribution of childhood leukaemias and non-Hodgkin lymphomas near nuclear installations in England and Wales. *Br Med J*, **309**, 501–5.

Black D (1984). Investigation of the possible increased incidence of cancer in West Cumbria. Report of the Independent Advisory Group. HMSO, London.

Black R J, Sharp L, Harkness E F and McKinney P A (1994). Leukaemia and non-Hodgkin lymphoma, incidence in children and young adults resident in the Dounreay area of Caithness, Scotland in 1968–91. *J Epidemiol Comm Hlth,* **48**, 232–6.

Boffetta P, Tredanie J and Greco A (2000). Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoking, a meta-analysis. *Environ Health Perspect,* **108,** 73–82.

Bogdanovic G, Jernberg L A, Priftakis P, Grillner L and Gustafsson B (2004). Human herpes virus 6 or Epstein-Barr virus were not detected in Guthrie cards from children who later developed leukaemia. *Br J Cancer,* **31,** 913–15.

Brooks D R, Mucci L A, Hatch E E and Cnattingius S (2004). Maternal smoking during pregnancy and risk of brain tumours in the offspring. A prospective study of 1.4 million Swedish births. *Cancer Causes Control*, **15**, 997–1005.

Busby C, Dorfman P, Rowe H and Kocjan B (2001). Cancer mortality and proximity to Oldbury nuclear power station in Gloucestershire 1995–1999. Including all malignancies male and female, breast, prostate, lung and stomach cancer mortality. With an analysis of childhood leukaemia incidence in ages 0–4 between 1974 and 1990 in Welsh Areas of Residence near the power station. Occasional paper 2001/6. Green Audit, Aberystwyth, April 2001.

Carstairs V and Morris R (1989). Deprivation, mortality and resource allocation. *Comm Med,* **11**, 364–72.

Cartwright R A, Alexander F E, McKinney P A, Ricketts T J, Hayhoe F G J and Clayton D G C (1990). *Leukaemia and Lymphoma. An Atlas of Distribution within Areas of England and Wales 1984–88.* LRF, London.

Chan L C, Lam T H, Li C K, Lau Y L, Yuen H L, Lee C W, Ha S Y, Yuen P M, Leung N K, Patheal S L, Greaves M F and Alexander F E (2002). Is the timing of exposure to infection a major determinant of acute lymphoblastic leukaemia in Hong Kong? *Paediatr Perinat Epidemiol*, **16**, 154–65.

Colt J and Blair A (1998). Parental occupational exposure and risk of childhood cancer. *Environ Health Perspect,* **106,** 909–25.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (1986). First Report. The implications of the new data on the releases from Sellafield in the 1950s for the conclusions of the Report on the Investigation of the Possible Increased Incidence of Cancer in West Cumbria. HMSO, London.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (1988). Second Report. Investigation of the possible increased incidence of leukaemia in young people near the Dounreay Nuclear Establishment, Caithness, Scotland. HMSO, London.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (1989). Third Report. Report on the incidence of childhood cancer in the West Berkshire and North Hampshire area, in which are situated the Atomic Weapons Research Establishment, Aldermaston and the Royal Ordnance Factory, Burghfield. HMSO, London.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (1996). Fourth Report. The incidence of cancer and leukaemia in young people in the vicinity of the Sellafield site, West Cumbria, further studies and an update of the situation since the publication of the Black Advisory Group in 1984. Department of Health, London.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (1999). Sixth Report. A reconsideration of the possible health implications of the radioactive particles found in the general environment around the Dounreay Nuclear Establishment in the light of the work undertaken since 1995 to locate their source. NRPB, Chilton.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (2002). Seventh Report. Parents occupationally exposed to radiation prior to the conception of their children. A review of the evidence concerning the incidence of cancer in their children. NRPB, Chilton.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (2005). Tenth Report. The incidence of childhood cancer around nuclear installations in Great Britain. Health Protection Agency, Chilton.

Committee on Medical Aspects of Radiation in the Environment (COMARE) and Radioactive Waste Management Advisory Committee (RWMAC) (1995). Potential health effects and possible sources of radioactive particles found in the vicinity of the Dounreay nuclear establishment. HMSO, London.

Cordier S, Monfort C, Filippini G, Preston-Martin S, Lubin F, Mueller B A, Holly E A, Peris-Bonet R, McCredie M, Choi W, Little J and Arslan A (2004). parental exposure to polycyclic aromatic hydrocarbons and the risk of childhood brain tumors, the SEARCH International Childhood Brain Tumor Study. *Am J Epidemiol*, **159**, 1109–16.

Court Brown W M, Doll R, Spiers F W, Duffy B J, Spiers F W, Duffy B J and McHugh (1960). Geographical variation in leukaemia mortality in relation to background radiation and other factors. *Br Med J,* **5188**, 1753–9.

Darby S C and Doll R (1987). Fallout, radiation doses near Dounreay, and childhood leukaemia. *Br Med J*, **294**, 603–7.

Dickinson H O and Parker L (1999). Quantifying the effect of population mixing on childhood leukaemia risk, the Seascale cluster. *Br J Cancer*, **81**, 144–51.

Diggle P J, Chetwynd A G, Haggkvist R and Morris S E (1995). Second-order analysis of space–time clustering. *Stat Methods Med Res*, **4**, 124–36.

Dockerty J D, Skegg D C G, Elwood J M, Herbison G P, Becroft D M and Lewis M E (1999). Infections, vaccinations, and the risk of childhood leukaemia. *Br J Cancer*, **80**, 1483–9.

Dockerty J D, Draper G, Vincent T, Rowan, S D and Bunch K J (2001). Case–control study of parental age, parity and socioeconomic level in relation to childhood cancers. *Int J Epidemiol*, **30**, 1428–37.

Dorling D (1991). The visualisation of spatial social structure. PhD thesis, Department of Geography, University of Newcastle.

Draper G J (ed) (1991). The geographical epidemiology of childhood leukaemia and non-Hodgkin lymphomas in Great Britain, 1966–83. Studies on Medical and Population Subjects No. 53, OPCS, HMSO, London.

Draper G J, Stiller C A, Cartwright R A, Craft A W and Vincent T J (1993). Cancer in Cumbria and in the vicinity of the Sellafield nuclear installation, 1963–90. *Br Med J*, **306**, 89–94.

Ewings P D, Bowie C, Philips M J and Johnson S A N (1989). Incidence of leukaemia in young people in vicinity of Hinkley Point nuclear power station, 1959–86. *Br Med J,* **299**, 289–93.

Feltbower R G, Pearce M S, Dickinson H O, Parker L and McKinney P A (2001). Seasonality of birth for cancer in Northern England, UK. *Paediatr Perinat Epidemiol*, **15**, 338–45.

Flower K B, Hoppin J A, Lynch C F, Blair A, Knott C, Shore D L and Sandler D P (2004). Cancer risk and parental pesticide application in children of agricultural health study participants. *Environ Health Perspect*, **112**, 631–5.

Gail M H and Benichou J (2000). *Encyclopedia of Epidemiologic Methods*. Chichester, John Wiley and Sons.

Gardner M J, Snee M P, Hall A J, Powell C A, Downes S and Terrell J D (1990). Results of case–control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J,* **300**, 423–9.

Garte S, Taioli E, Crosti F, Sainati L, Barisone E, Luciani M, Jankovic M and Biondi A G (2000). Deletion of parental GST genes as a possible susceptibility factor in the etiology of infant leukemia. *Leuk Res,* **24**, 971–4.

Gilham C, Peto J and Simpson J (2005). Day care in infancy and risk of childhood acute lymphoblastic leukaemia, findings for UK case control study. *Br Med J*, **330**, 1294.

Giusti R, Iwamoto K and Hatch E (1995). Diethylstilboestrol revisited, a review of the long term health effects. *Ann Intern Med*, **122**, 778–88.

Greaves M F (1988). Speculations on the cause of childhood acute lymphoblastic leukemia. *Leukemia*, **2,** 120–25.

Greaves M F (1997). Aetiology of acute leukaemia. *Lancet*, **349,** 344–9.

Greaves M F and Alexander F E (1993). An infectious etiology for common acute lymphoblastic leukemia in childhood? *Leukemia*, **7**, 349–60.

Greaves M F and Wiemels J (2003). Origins of chromosome translocations in childhood leukaemia. *Nature Rev Cancer*, **3**, 639–49.

Groves F D, Gridley G, Wacholder S, Shu X O, Robison L L, Neglia J P and Linet M S (1999). Infant vaccinations and risk of childhood acute lymphoblastic leukaemia in the USA. *Br J Cancer*, **81**, 175–8.

Hasle H (2001). Patterns of malignant disorder in individuals with Downs syndrome. *Lancer Oncol*, **2**, 429–36.

Heasman M A, Kemp I W, Urquhart J D and Black R (1986a). Childhood leukaemia in Northern Scotland. *Lancet,* **1**, 266.

Heasman M A, Kemp I W, Urquhart J D and Black R (1986b). Leukaemia and lymphatic cancer in young people near nuclear installations. *Lancet,* **1**, 385.

Heath C W Jr (2005). Community clusters of childhood leukemia and lymphoma: evidence of infection? *Am J Epidemiol,* **162**, 817–22.

Heath C W Jr and Hasterlik R J (1963). Leukaemia among children in a suburban community. *Am J Med*, **34**, 796–812.

Higgins C D, dos-Santos-Silva I, Stiller C A and Swerdlow A J (2001). Season of birth and diagnosis of children with leukaemia, an analysis of over 15,000 UK cases occurring from 1953–95. *Br J Cancer*, **84**, 406–12.

Hooper M L (1999). Is sunlight an aetiological agent in the genesis of retinoblastoma? *Br J Cancer*, **79**, 1273–6.

Huncharek M and Kupelnick B (2004). A meta-analysis of maternal cured meat consumption during pregnancy and the risk of childhood brain tumors. *Neuroepidemiology*, **23**, 78–84.

Infante-Rivard C, Fortier I and Olson E (2000). Markers of infection, breast-feeding and childhood acute lymphoblastic leukaemia. *Br J Cancer*, **83**, 1559–64.

Jarrett R F (2003). Risk factors for Hodgkin lymphoma by EBV status and significance of detection of EBV genomes in serum of patients with EBV-associated Hodgkin lymphoma. *Leuk Lymphoma*, **44**, Suppl 3, S27–32.

Jemal A, Devesa S S, Fears T R and Fraumeni J F (2000). Retinoblastoma incidence and sunlight exposure. *Br J Cancer*, **82**, 1875–8.

Kauppi M, Savolainen H, Anttila V and Isomaki H (1996). Increased risk of leukaemia patients with juvenile chronic arthritis treated with chlorambucil. *Acta Paediatric,* **85**, 248–50.

Kinlen L J (1988). Evidence for an infective cause of childhood leukaemia, comparison of a Scottish new town with nuclear processing sites in Britain. *Lancet,* **2**, 1323–7.

Kinlen L J (1995). Epidemiological evidence for an infective basis in childhood leukemia. *Br J Cancer*, **71**, 1–5.

Kinlen L and Doll R (2004), Population mixing and childhood leukaemia: Fallon and other US clusters. *Br J Cancer,* **91**, 1–3.

Knox E G (1964). The detection of space–time interactions. *Appl Stats*, **13**, 25–9.

Knox E G (2005a). Childhood cancers and atmospheric carcinogens. *J Epidemiol Comm Health*, **59**, 101–5.

Knox E G (2005b). Oil combustion and childhood cancer. *J Epidemiol Comm Health*, **59**, 755–60.

Knox E G (2006). Roads, railways, and childhood cancer. *J Epidemiol Comm Health*, **60,** 136–41.

Krajinovic M, Sinnett H, Richer C, Labuda D and Sinnett D (2002). Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. *Int J Cancer*, **97**, 230–36.

Kroll M E, Draper G J, Stiller C A and Murphy M F (2006). Childhood leukaemia incidence in Britain, 1974–2000: time trends and possible relation to influenza epidemics. *J Natl Cancer Inst,* **98**, 417–20.

Kwan M L, Block G, Selvin S, Month S and Buffler P A (2004). Food consumption by children and the risk of childhood acute leukemia. *Am J Epidemiol,* **160,** 1098–107.

Laurier D, Valenty M and Tirmarche M (2001). Radon exposure and the risk of leukemia, a review of epidemiological studies. *Health Phys,* **81**, 272–88.

Law G R, Parslow R C and Roman E (2003). Childhood cancer and population mixing. *Am J Epidemiol*, **158**, 328–36.

Lehtinen M, Koskela P, Ogmundsdottir H M, Bloigu A, Dillner J, Gudnadottir M, Hakulinen T, Kjartansdottir A, Kvernung M, Pukkala E, Tulinius H and Lehtinen T (2003). Maternal herpesvirus infections and risk of acute lymphoblastic leukemia in the offspring. *Am J Epidemiol*, **158**, 207–13.

Lehtinen M, Ogmundsdottir H M, Bloigu A, Hakulinen T, Hemminki E, Gudnadottir M, Kjartansdottir A, Paavonen J, Pukkala E, Tulinius H, Lehtinen T and Koskela P (2005). Associations between three types of maternal bacterial infection and risk of leukemia in the offspring. *Am J Epidemiol*, **162**, 662–7.

Leman J A, Evans A, Mooi W and MacKie R M (2005). Outcomes and pathological review of a cohort of children with melanoma. *Br J Dermatol*, **152**, 1321–3.

Little J (1999). *Epidemiology of Childhood Cancer.* IARC Scientific Publications No. 149. International Agency for Research on Cancer, Lyon.

Ma X, Does M B, Metayer C, Russo C, Wong A and Buffler P A (2005). Vaccination history and risk of childhood leukaemia. *Int J Epidemiol*, **34,** 1100–109.

MacKenzie J, Gallagher A, Clayton R A, Perry J, Eden O B, Ford A M, Greaves M F and Jarrett R F (2001). Screening for herpesvirus genomes in common acute lymphoblastic leukemia. *Leukemia*, **15**, 415–21.

McKinney P A, Cartwright R A, Saiu J M T, Mann J R, Stiller C A, Draper G J, Hartley A L, Hopton P A, Birch J M, Waterhouse J A H and Johnston H E (1987). The Inter-regional Epidemiological Study of Childhood Cancer (IRESCC), a case control study of aetiological factors in leukaemia and lymphoma. *Arch Dis Childhood*, **62**, 279–87.

McKinney P A, Ironside J W, Harkness E F, Arango J C, Doyle D and Black R J (1994). Registration quality and descriptive epidemiology of childhood brain tumours in Scotland 1975–90. *Br J Cancer,* **70**, 973–9.

McKinney P A, Juszczak E, Findlay E, Smith K and Thomson C S (1999). Pre- and perinatal risk factors for childhood leukaemia and other malignancies, a Scottish case control study. *Br J Cancer*, **80**, 1844–51.

McKinney P A, Fear N T and Stockton D on behalf of the UK Childhood Cancer Study Investigators (2003a). Parental occupation at periconception: findings from the United Kingdom Childhood Cancer Study. *Occup Environ Med*, **60**, 901–9.

McKinney P A, Feltbower R G, Parslow R C, Lewis I J, Glaser A W and Kinsey S E (2003b). Patterns of childhood cancer by ethnic group in Bradford, UK 1974–1997. *Eur J Cancer*, **39**, 92–7.

McNally R J Q and Eden O B (2004). An infectious aetiology for childhood acute leukaemia, a review of the evidence. *Br J Haematol*, **127,** 243–63.

McNally R J Q, Cairns D P, Eden O B, Alexander F E, Taylor G M, Kelsey A M and Birch J M (2002a). An infectious aetiology for childhood brain tumours? Evidence from space–time clustering and seasonality analyses. *Br J Cancer*, **86**, 1070–77.

McNally R J Q, Alexander F E and Birch J M (2002b). Space–time clustering analyses of childhood acute lymphoblastic leukaemia by immunophenotype. *Br J Cancer*, **87**, 513–15.

McNally R J Q, Kelsey A M, Eden O B, Alexander F E, Cairns D P and Birch J M (2003a). Space–time clustering patterns in childhood solid tumours other than central nervous system tumours. *Int J Cancer* **103**, 253–8.

McNally R J Q, Alston R D, Cairns D P, Eden O B, Kelsey A M and Birch J M (2003b). Geographical and ecological analyses of childhood Wilms' tumours and soft-tissue sarcomas in North West England. *Eur J Cancer*, **39**, 1586–93.

McNally R J Q, Alexander F E, Eden O B and Birch J M (2004). Little or no space–time clustering found amongst cases of childhood lymphoma in North West England. *Eur J Cancer*, **40**, 585–9.

Moore L E, Gold L, Stewart P A, Gridley G, Prince J R and Zahm S H (2005). Parental occupational exposures and Ewing's sarcoma. *Int J Cancer*, **114**, 472–8.

Muirhead C R and Ball A M (1989). Contribution to the discussion of the Royal Statistical Society meeting on cancer near nuclear installations. *J R Statist Soc, Series A*, **152**, 376.

Muirhead C R and Butland B K (1996). Testing for over-dispersion using an adapted form of the Potthoff-Whittinghill method. IN *Methods for Investigating the Localized Clustering of Disease* (F E Alexander and P Boyle, eds), pp 40–52 and 162–163. IARC Scientific Publication No. 135. International Agency for Research on Cancer, Lyon.

Narod S A, Hawkins M M, Robertson C M and Stiller C A (1997). Congenital anomalies and childhood cancer in Great Britain. *Am J Hum Gent,* **60**, 474–85.

Neglia J P, Linet M S, Shu X O, Severson R K, Potter J D, Mertens A C, Wen W, Kersey J H and Robison L L (2000). Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia. *Br J Cancer*, **82**, 234–40.

Olsen J H, Boice J D and Fraumeni J F (1990). Cancer in children of epileptic mothers and the possible relation to maternal anti-convulsant therapy. *Br J Cancer,* **62**, 996–9.

Orjuela M, Ponce Castaneda V, Ridaura C, Lecona E, Leal C, Abramson D H, Orlow I, Gerald W and Cordon-Cardo C (2000). Presence of human papilloma virus in tumor tissue from children with retinoblastoma: an alternative mechanism for tumor development. *Clin Cancer Res*, **6**, 4010–16.

Pang D, McNally R and Birch J M (2003). Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. *Br J Cancer*, **88**, 373–81.

Parkin D M, Kramarova E, Draper G J, Masuyer E, Michaeis J, Neglia J, Qureshi S and Stiller C A (1998). International Incidence of Childhood Cancer, Volume 2. IARC Scientific Publications No. 144. International Agency for Research on Cancer, Lyon.

Parkin M, Pisani P, Munoz N and Ferlay J (1999). The global health burden of infection associated cancer. *Cancer Survey*, **33**, 5–33.

Petridou E, Kassimos D, Kalmanti M, Kosmidis H, Haidas S, Flytzani V, Tong D and Trichopoulos D (1993). Age of exposure to infections and risk of childhood leukaemia. *Br Med J*, **307**, 774.

Potthoff R F and Whittinghill M (1966). Testing for homogeneity, II. The Poisson distribution. *Biometrika*, **53**, 183–90.

Priftakis P, Dalianis T, Carstensen J, Samuelsson U, Lewensohn-Fuchs I, Bogdanovic G, Winiarski J and Gustafsson B (2003). Human polyomavirus DNA is not detected in Guthrie cards (dried blood spots) from children who developed acute lymphoblastic leukemia. *Med Pediatr Oncol*, **40**, 219–23.

Reynolds P, Von Behren J, Gunier R B, Goldberg D E and Hertz A (2004). Residential exposure to traffic in California and childhood cancer. *Epidemiology*, **15**, 6–12.

Reynolds P, Von Behren J, Gunier R B, Goldberg D E, Harnly M and Hertz A (2005). Agricultural pesticide use and childhood cancer in California. *Epidemiology*, **16**, 93–100.

Roman E, Beral V, Carpenter L, Watson A, Barton C, Ryder H and Aston D L (1987). Childhood leukaemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities in relation to nuclear establishments in the vicinity. *Br Med J*, **294**, 597–602.

Roman E, Fear N, Ansell P, Bull D, Draper G, McKinney P, Michaelis J, Passmore J and von Kries R (2002). Vitamin K and childhood cancer – analysis from individual patient data from six case control studies. *Br J Cancer,* **86,** 63–9.

Ron E, Lubin J, Shore R E, Mabuchi K, Modan B, Pottern L M, Schneider A B, Tucker M A and Boice J D Jr (1995). Thyroid cancer after exposure to external irradiation, a pooled analysis of seven studies. *Radiat Res,* **141,** 259–77.

Rosenbaum P F, Buck G M and Brecher M L (2005). Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia. *Paediatr Perinat Epidemiol*, **19**, 152–64.

Ross J A, Severson R K, Swensen A R, Pollock B H, Gurney J G and Robison L L (1999). Seasonal variations in the diagnosis of childhood cancer in the United States. *Br J Cancer*, **81**, 549–53.

Schüz J, Kaletsch U, Meinert R, Kaatsch P and Michaelis J (1999). Association of childhood leukaemia with factors related to the immune system. *Br J Cancer,* **80,** 585–90.

Sharp L, Black R J, Harkness E and McKinney PA (1996). Incidence of childhood leukaemia and non-Hodgkin lymphoma in the vicinity of nuclear sites in Scotland, 1968–93. *Occup Environ Med*, **53**, 823–31.

Sharp L, McKinney P A and Black R J (1999). Incidence of childhood brain and other non-haematopoietic neoplasms near nuclear sites in Scotland, 1975–94. *Occup Environ Med*, **56**, 308–14.

Shibata Y, Yamashita S, Masayakin V B, Panasyuk G D and Nagataki S (2001). 15 years after Chernobyl – new evidence of thyroid cancer. *Lancet,* **358,** 1965–6.

Shu X O, Gao Y T and Brinton L A (1988). A population based case–control study of childhood leukemia in Shanghai. *Cancer,* **62,** 635–44.

Skinner J, Mee T J, Blackwell R P, Maslanyi M P, Simpson J, Allen S G, Day N E, Cheng K K, Gilman E, Williams D, Cartwright R, Craft A, Birch J M, Eden O B, McKinney P A, Deacon J, Peto J, Beral V, Roman E, Elwood P, Alexander F E, Mott M, Chilvers C E, Muir K, Doll R, Taylor C M, Greaves M, Goodhead D, Fry F A, Adams G and Law G (United Kingdom Childhood Cancer Study Investigators) (2002). Exposure to power frequency electric fields and the risk of childhood cancer in the UK. *Br J Cancer,* **18**, 1257–66.

Smith M A, Chen T and Simon R (1997). Age-specific incidence of acute lymphoblastic leukemia in US children, *in utero* initiation model. *J Natl Cancer Inst*, **89**, 1542–4.

Smith M A, Simon R, Strickler H D, McQuillan G, Ries L A and Linet M S (1998). Evidence that childhood acute lymphoblastic leukemia is associated with an infectious agent linked to hygiene conditions. *Cancer Causes Control*, **9**, 285–98.

Smith M A, Strickler H D, Granovsky M, Reaman G, Linet M, Daniel R and Shah K V (1999). Investigation of leukemia cells from children with common acute lymphoblastic leukemia for genomic sequences of the primate polyomaviruses JC virus, BK virus, and simian virus 40. *Med Pediatr Oncol*, **33**, 441–3.

Steinmaus C, Lu M, Todd R L and Smith A H (2004). Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other US military aviation facilities. *Environ Health Perspect*, **112**, 766–71.

Stewart A, Webb J and Hewitt D (1958). A survey of childhood malignancies. *Br Med J,* **30,** 1495–508.

Stiller C (2004a). Aetiology and epidemiology. In *Paediatric Oncology* (R Pinkerton, P Plowman and R Pieter R, eds), pp 3–24. Arnold, London.

Stiller C A (2004b). Epidemiology and genetics of childhood cancer. *Oncogene,* **23**, 6429–44.

Stiller C A and Boyle P J (1996). Effect of population mixing and socioeconomic status in England and Wales, 1979–85, on lymphoblastic leukaemia in children. *Br Med J*, **313**, 1297–300.

Stiller C A, Draper G J, Vincent T J and O'Connor C M (1991). Incidence rates nationally and in administratively defined areas. In *The Geographical Epidemiology of Childhood Leukaemia and Non-Hodgkin Lymphomas in Great Britain, 1966–83.* Studies on Medical and Population Subjects No. 53, OPCS (G Draper, ed), pp 25–35. HMSO, London.

Stiller C A, Chessells J M and Fitchett M (1994). Neurofibromatosis and childhood leukaemia/lymphoma: a population-based UKCCSG study. *Br J Cancer*, **70,** 969–72.

Stiller, C A, Allen M B, and Eatock E M (1995). Childhood cancer in Britain, The National Registry of Childhood Tumours and incidence rates 1978–87. *Eur J Cancer* **31A**, 2028–34.

Taylor G M, Dearden S, Payne N, Ayres M, Gokhale D A, Birch J M, Blair V, Stevens R F, Will A M and Eden O B (1998). Evidence that an HLA DQA1-DQB1 haplotype influences susceptibility to childhood cancer acute lymphoblastic leukaemia in boys provides further support for a infection related aetiology. *Br J Cancer,* **78,** 561–5.

Taylor G M, Dearden S, Ravetto P, Ayres M, Watson P, Hussain A, Birch J, Greaves M, Eden O B and UKCCS Investigators (2002). Genetic susceptibility to childhood common acute lymphoblastic leukaemia is associated with polymorphic peptide-binding pocket profiles in HLA-DPB1*0201. *Hum Mol Genet*, **11**, 1585–97.

UK Childhood Cancer Study (UKCCS) Investigators (2001). Breastfeeding and childhood cancer. *Br J Cancer*, **85**, 1685–94.

UK Childhood Cancer Study (UKCCS) Investigators (2002). The United Kingdom Childhood Cancer Study of exposure to domestic sources of ionising radiation; 1: radon gas. *Br J Cancer,* **86**, 1721–6.

Van Steensel-Moll H A, Valkenburg H A and van Zanen G E (1986). Childhood leukemia and infectious diseases in the first year of life, a register-based case–control study. *Am J Epidemiol*, **124**, 590–94.

Varley J M, Evans D G, and Birch J M (1997). Li Fraumeni syndrome – a molecular and clinical review. *Br J Cancer*, **76**, 1–14.

Wartenberg D, Schneider D and Brown S (2004). Childhood leukaemia incidence and the population mixing hypothesis in US SEER data. *Br J Cancer,* **90**, 1771–6.

Westerbeek R M, Blair V, Eden O B, Kelsey A M, Stevens R F, Will A M, Taylor G M and Birch J M (1998). Seasonal variations in the onset of childhood leukaemia and lymphoma. *Br J Cancer*, **78**, 119–24.

Westergaard T, Andersen P K, Pedersen J B, Olsen J H, Frisch M, Sorensen H T, Wohlfahrt J and Melbye M (1997). Birth characteristics, sibling patterns, and acute leukemia risk in childhood, a population-based cohort study. *J Natl Cancer Inst*, **89**, 939–47.

WHO (World Health Organisation) (1990). *International Classification of Diseases for Oncology,* Second Edition (C Percy, V Van Holten and C Muir, eds). World Health Organisation, Geneva.

Wiemels J L, Cazzaniga G, Daniotti M, Eden O B, Addison G M, Masera G, Saha V, Biondi A and Greaves M F (1999). Prenatal origin of acute lymphoblastic leukaemia in children. *Lancet*, **354**, 1499–503.

Yuan X J, Gu L J, Xue H L, Tang J Y, Zhao J C, Chen J, Wang Y P, Chen J, Pan C and Song D L (2003). Analysis on GST-Pi genetic polymorphism in children with acute leukaemia. *Zhonghua Yi Xue Za Zhi*, **83**, 1863–6.

Zahm S H and Ward M H (1998). Pesticides and childhood cancer. *Environ Health Persp,* **106,** 893–908.

ACKNOWLEDGEMENTS

We are grateful to the many consultants and general practitioners who routinely provide the information upon which the NRCT is based, and to the Office for National Statistics, the Information and Statistics Division of the Common Services Agency of the Scottish Health Service, the Registrar-General for Scotland, the regional cancer registries and the UK Children's Cancer Study Group.

THE APPENDICES

APPENDIX A

GLOSSARY

AETIOLOGY The study of causes of disease.

AGE-STANDARDISED RATES (ASRs) For the purposes of this report, for ages 0–14 years, age-standardised rates (ASRs) have been calculated as simple averages of the age-specific incidence rates for the five-year age groups they contain. This is equivalent to standardising to a uniform population (with equal numbers in each five-year age group).

ALL *See Leukaemia.*

AML *See Leukaemia.*

CASE–CONTROL STUDY A study in which the risk factors of a group of individuals identified as having the disease, the *cases*, are compared to those for a group of individuals not having the disease, the *controls*.

CENSUS The enumeration of an entire population, usually with details being recorded on residence, age, sex, occupation, ethnic group, marital status, birth history, and relationship to head of household.

CLL *See Leukaemia.*

COHORT STUDY This is a method used in analytical epidemiology. A cohort study is designed to answer the question, 'What are the effects of a particular exposure?' Cohort studies compare a group of individuals with the exposure under consideration to a group without the exposure, or with a different level of exposure, or to the country as a whole. The groups (cohorts) are followed over a period of time, and the disease occurrence is compared between the groups or between the cohort and rates expected from national statistics.

CONFIDENCE INTERVAL Indicates the (im)precision of the study findings in measuring the true size of any risk. In this way a confidence interval conveys the effects of sampling variation on the precision of, for example, age-standardised rates calculated from a limited time period, etc. Specifically, the true rate will be inside the 95% confidence interval on 95% of occasions, although the observed rate remains the best estimate of the true value.

CONFOUNDING Confounding is a problem in epidemiological studies which arises when there is an exposure which is associated with both the factor that is being investigated and the disease under study. This would give rise to an apparent relationship between the factor being investigated and the disease, even if the factor did not cause the disease. For example, suppose lung cancer was being studied in workers exposed to a particular chemical. If those exposed to higher levels of the chemical smoked more than other workers, then the chemical would be associated with lung cancer even if it did not actually cause the disease. The problem can be addressed in the design and analysis of studies but requires that data on the confounder be collected.

DNA	A chemical made up of a linear sequence of different molecules called bases (Adenine, Thymine, Cytosine and Guanine) constituting the genetic material of organisms. There are four bases and the permuted sequence of these is read as a code which determines the composition and properties of the organism. The simplest organisms such as bacteria have nearly five million bases in their genetic material, humans have more than three-hundred million bases.
ENDEMIC	A disease that is constantly present to a greater or lesser degree in people of a certain class or in people living in a particular location.
EPIDEMIC	A widespread outbreak of an infectious disease; many people are infected at the same time.
EPSTEIN-BARR VIRUS (EBV)	EBV is a common human virus that causes infectious mononucleosis and is also associated with various types of human cancers.
EXTRA-POISSON VARIATION (EPV)	If cases of disease arise randomly within the population at risk then the number of cases within small areas would be expected to follow a Poisson distribution (one well-known type of statistical distribution). The variance of this number would then be the same as the mean (the expected number). If the disease risk were greater in some small areas than in others, then the variance of these numbers will be higher than that predicted by the Poisson distribution. This is *extra-Poisson variation (EPV)*. The extent by which the variance exceeds the Poisson mean is a *measure* of the magnitude of the extra-Poisson variation. For example, the EPV would equal 0.1 if the variance were 10% larger than the Poisson mean.
GERM CELL	These are the cells which in the human are present in the ovary or testicles and which divide to become the egg or sperm. In this division only one-half of all the chromosomes are included in the final cell so that when the egg and sperm come together there will be a full chromosome content.
GERM LINE	Usually used to refer to those cells called germ cells as well as the final egg and sperm.
HODGKIN LYMPHOMA	A form of malignant lymphoma that is characterised by painless enlargement of lymphatic tissue and the spleen and often involves symptoms such as fever, wasting weight loss, anaemia, and night sweats.
INCIDENCE	The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. More generally, the number of new events, eg new cases of disease in a defined population, within a specified period of time. The term incidence is sometimes used to denote 'incidence rate'.
INFECTIOUS AETIOLOGY	The process by which disease is brought about by a transmissible agent, eg a virus.
KAPOSI SARCOMA	A cancer characterised by bluish-red nodules on the skin, usually on the lower extremities, that often occurs in people with AIDS. Human herpes virus 8 (HHV8) is the causative agent of Kaposi's sarcoma.
LEUKAEMIA	A group of malignant diseases of the blood-forming tissues in which normal control of cell production breaks down and the cells that are produced are abnormal. Leukaemia can be classified as either lymphoid or myeloid and as either acute or chronic (eg ALL, AML, CLL and CML). Lymphoid and myeloid refer to the type of white cell affected. If this is a lymphocytic cell the condition is called lymphocytic or lymphoblastic leukaemia. Myeloid leukaemias affect

any of the other types of white blood cells or the red cell or platelet producing cells. Acute leukaemias develop quickly and progress rapidly; chronic leukaemias are slower to develop and slower to progress.

LYMPHOCYTE A type of white blood cell that is part of the body's immune system.

LYMPHOMA A malignant tumour of the lymphatic system (lymph nodes, reticulo-endothelial system and lymphocytes).

MALIGNANCY Cancerous growth, a mass of cells showing uncontrolled growth, a tendency to invade and damage surrounding tissues and an ability to seed daughter growths to sites remote from the primary growth.

MLL GENE In acute leukaemia, the myeloid/lymphoid or mixed lineage leukaemia (MLL) gene located on chromosome 11q23, is a recurrent target of chromosome translocation. MLL gene rearrangements occur in both subtypes of leukaemia ALL (acute lymhoblastic leukaemia) and AML (acute myeloid leukaemia).

MULTIPLE SIGNIFICANCE TESTING *See Statistical significance.*

NEAREST NEIGHBOUR A technique of determining whether a set of points in space is distributed in a regular, random or clustered pattern by comparing the mean distance of points from their nearest neighbours to the value expected if the pattern were random.

NON-HODGKIN LYMPHOMA (NHL) A group of lymphomas which differ in important ways from Hodgkin lymphoma and are classified according to the microscopic appearance of the cancer cells. In children, NHL and leukaemias are often combined due to historical difficulties in making diagnostic distinctions.

NULL HYPOTHESIS The statistical hypothesis that one variable has no association with another variable or set of variables, or that two or more population distributions do not differ from one another.

P-VALUE A p-value provides an idea of the strength of the evidence against the null hypothesis. A low p-value points to rejection of the null hypothesis. For a significance test at the 5% level, any result giving a p-value less than 0.05 would be regarded as significant and lead to rejection of the null hypothesis in favour of an alternative hypothesis.

PARENTAL PRECONCEPTIONAL IRRADIATION (PPI) A hypothesis suggesting that radiation-induced mutations in the germ line cause a predisposition to leukaemia or NHL in the next generation.

PEER REVIEW Peer review is a process used in the publication of manuscripts and in awarding funding for research. Publishers (scientific and medical journals, and books) and funding agencies use peer review to select and to screen submissions. The process also assists authors in meeting the standards of their discipline. Publications and awards that have not undergone peer review are liable to be regarded with suspicion by professionals in many fields. Peer review subjects an author's work or ideas to the scrutiny of one or more others who are experts in the field. These referees each return an evaluation of the work, including suggestions for improvement, to an editor or other intermediary (typically, most of the referees' comments are eventually seen by the author as well).

POISSON DISTRIBUTION The Poisson distribution is a probability distribution for numbers of events – for example, the number of cancers within an area. The mean and variance of counts that follow the Poisson distribution are the same.

POPULATION MIXING The population mixing hypothesis proposes that childhood leukaemia can be a rare response to a common but unidentified infection (hence the absence of marked space–time clustering). Epidemics of this (mainly sub-clinical) infection are prompted by influxes of people into rural areas, where susceptible individuals are more prevalent than the average. Such inflexes would increase population density and hence the level of contacts between susceptible and infected individuals, thereby increasing the risk of childhood leukaemia.

POTTHOFF-WHITTINGILL TEST A test for extra-Poisson variation that is related to the variance-to-mean ratio. *(See extra-Poisson variation.)*

RATE RATIO A comparison of two groups in terms of incidence rates, person–time rates, or mortality rates.

RECALL BIAS This is a source of bias due to differential recall by cases and controls. In many case–control studies retrospective information is obtained by interviewing the subjects or their relatives. People with a particular disease or condition may have thought a lot about a possible link with past events, especially with respect to widely publicised risk factors. Their recall of past events may differ from that of people without the disease or condition under study.

RELATIVE RISK (RR) A ratio of the risk of disease or death among those exposed to a potential hazard to the risk among those not exposed to the hazard.

RETINOBLASTOMA Retinoblastoma is a rare childhood cancer of the eye and usually appears in infants or young children. In Western countries it occurs at a frequency of about one in every 20,000 births. The disease is heritable in about 40% of cases. In a minority of cases, there is a family history of the disease.

RISK The probability that an event will occur, eg that an individual will become ill or die within a stated period of time or age. Also, a non-technical term encompassing a variety of measure of the probability of a (generally) unfavourable outcome. *(See Relative risk.)*

SIGNIFICANCE TEST A result that lies outside the range of values expected to occur, if some specified hypothesis is true, is said to be statistically significant. A probability (p-value) of 0.05 for such an occurrence is commonly used to separate 'significant' from 'non-significant' results. This boundary is arbitrary.

SOCIO-DEMOGRAPHIC Characteristics that relate to social or demographic (population) variables, such as age, socio-economic status (SES), degree of household overcrowding or population density.

SOCIO-ECONOMIC STATUS (SES) A measure related to levels of living or social class. May apply to individuals or groups. In this report it is applied to the populations of census wards or county districts, and is based on information from the 1981 census.

STATISTICAL SIGNIFICANCE AND MULTIPLE SIGNIFICANCE TESTING In an investigation of, for example, whether exposure to a particular agent is associated with a certain type of cancer, statistical tests will be carried out to assess the probability that a result at least as extreme as that observed could have arisen by chance. Researchers will commonly describe a result as statistically significant if the probability that it arose by chance is 5% or less (see also p-value).

If associations between the agent and two distinct types of cancer are tested, then, in the absence of any underlying affect, the chance that one of these tests will achieve statistical significance as defined above would be about 10%. If three or more tests are carried out, the probability that one of the p-values is 5% or less becomes even greater. Unless there is a special reason (a 'prior hypothesis') to suggest that one particular type of cancer may be associated with exposure to the agent, it is difficult to interpret the individual p-values. The usual assumption, that a p-value of less than 5% is likely to reflect causation rather than chance, is inappropriate because the multiple significance testing means that an apparently significant result has an increased probability of arising by chance.

STANDARDISED INCIDENCE RATIO (SIR)

As standardised mortality ratio, but referring to the incidence of disease rather than death.

STANDARDISED MORTALITY RATIO (SMR)

The ratio of the number of deaths in the study group or population to the expected number. The expected number is calculated using the age- and sex-specific death rates for a reference population. These 'reference rates' will often be those of the national population but may also be taken from a smaller area (eg the south west of England or Cumbria).

TREND

Movement in one direction (increase or decrease) of the values of a variable, either over a period of time, or in relation to distance from the location being analysed.

VIRUS

A biological entity that can reproduce only within a host cell. Viruses consist of nucleic acid *(see DNA)* covered by protein. Once inside the cell, the virus uses the capability of the host cell to produce more viruses.

APPENDIX B

COMMITTEE ON MEDICAL ASPECTS OF RADIATION IN THE ENVIRONMENT

CHAIRMAN

Professor A T Elliott BA PhD DSc CPhys FinstP FIPEM
Western Infirmary, Glasgow

DEPUTY CHAIRMAN

Professor R Waters BSc PhD DSc
Pathology Department
University of Wales College of Medicine, Cardiff

PRESENT MEMBERS

Professor Freda Alexander BA MSc PhD
Department of Community Health Services
University of Edinburgh

Professor T C Atkinson BSc PhD
Department of Geological Sciences
University College London

Dr H R Baillie-Johnson MB BS FRCR FRCP
Department of Oncology
Norfolk and Norwich University Hospital

Dr C J Gibson BA MSc PhD FIPEM
Medical Physics and Clinical Engineering
Oxford

Professor Shirley V Hodgson BM BCh DM FRCP
Department of Clinical Development Sciences
St George's University of London

Dr J Mackay MA MD FRCP CRCPE
Clinical Genetics Unit
Great Ormond St Hospital NHS Trust, London

Professor Patricia McKinney BSc PhD MFPHM(Hon)
Paediatric Epidemiology Group
University of Leeds

Professor T J McMillan BSc PhD
Institute of Environmental and Natural Sciences
Lancaster University

Professor M D Mason MD FRCP FRCR
Oncology and Palliative Medicine
University of Wales College of Medicine

Dr C D Mitchell PhD FRCP
Paediatric Haematology/Oncology Unit
John Radcliffe Hospital, Oxford

Dr M Murphy BA MB BChir MSc FFPH
Childhood Cancer Research Group
University of Oxford

Professor Louise Parker BSc PhD FRCPH FFPM(Hon)
Sir James Spence Institute of Child Health
Newcastle University

Dr R A Shields MA MSc PhD FIPEM
Medical Physics Department
Manchester Royal Infirmary

Professor A M R Taylor BSc MSc PhD
Department of Cancer Studies
University of Birmingham

Professor J Thacker BSc PhD
MRC Radiation and Genome Stability Unit
Oxfordshire

Dr Julia Verne BSc MSc MB BS PhD FFPH
Regional Public Health Group
Government Office for the South West (Bristol)

Professor E Wright HNC BSc PhD CBiol MIBiol MRCPath FRCPath
Department of Molecular and Cellular Pathology
University of Dundee

FORMER MEMBERS WHO SERVED DURING THE PREPARATION OF THIS REPORT

Professor B A Bridges OBE BSc PhD CBiol FIBiol
Genome Damage and Stability Centre
University of Sussex
Brighton *(until March 2005)*

Professor R A Cartwright BA MB BChir MA PhD FFOM FFPHM
Leukaemia Research Fund Centre for Epidemiology
University of Leeds *(until March 2003)*

Professor K K Cheng BSc MB BS PhD MFPHM MRCGP FHKCCM FHKAM
Department of Public Health and Epidemiology
University of Birmingham *(Until March 2000)*

Professor Sarah Darby BSc MSc PhD
Clinical Trial Service Unit
University of Oxford *(Until March 2000)*

Dr G J Draper OBE MA DPhil FFPH
Childhood Cancer Research Group
University of Oxford *(until March 2003)*

Professor O B Eden MBBS D(Obst)RCOG MRCP(UK) FRCP (Edin) FRCP FRCPath FRCPCH
Academic Unit of Paediatric Oncology
Christie Hospital NHS Trust
Manchester *(until March 2003)*

Professor N Haites BSc PhD MBChB MRCPath
Department of Medical Genetics
University of Aberdeen (*until January 2005*)

Professor J Little BA MA PhD
Department of Medicine and Therapeutics
University of Aberdeen *(until May 2004)*

Dr Margaret Spittle OBE MSc MB BS MRCS FRCP FRCR DMRT AKC
Meyerstein Institute of Radiotherapy and Oncology
Middlesex Hospital *(until September 2004)*

SECRETARIAT

Dr R Hamlet BSc PhD CBiol MIBiol (Scientific)

Mr S Ebdon-Jackson BSc MSc HonMRCP (Scientific)

Dr Jill Meara MA MSc BMBCh FFPH (Medical)

Dr J R Cooper BSc DPhil (Scientific)

Dr C R Muirhead BSc MSc PhD (Scientific)

Miss Jane Bradley MRSC CChem (Minutes)

Dr Nezahat Hunter BSc Msc PhD (Minutes)

Dr Emma Boswell BSc PhD (Minutes)

Dr Kerry Broom BSc DPhil CBiol MIBiol (Minutes)

Miss Julie Kedward (Administrative)

ASSESSORS IN ATTENDANCE REPRESENTING THE FOLLOWING ORGANISATIONS

Department for the Environment, Food and Rural Affairs

Department of Health

Department of Health, Social Services and Public Safety (Northern Ireland)

Department of Trade and Industry

Environment Agency

Food Standards Agency

Health Protection Agency, Radiation Protection Division (formerly NRPB)

Health and Safety Executive

Information and Statistics Division, Common Services Agency, NHS Scotland

Medical Research Council

Ministry of Defence

Office for National Statistics

Scottish Environment Protection Agency

Scottish Executive

Welsh Assembly Government

GAS COMMITTEE

CHAIRMAN

Professor R Cartwright

MEMBERS

Professor Freda Alexander

Professor B A Bridges

Dr G Draper

Professor A Elliott

Dr M Murphy

Dr Julia Verne

FORMER COMMITTEE MEMBERS

Professor K K Cheng

Professor Neva Haites

Professor J Little

OTHER PERSONS WHO ASSISTED THE COMMITTEE

Dr J Bithell

Dr Estelle A Gilman

Mrs Mary Kroll

Dr R J McNally

Dr C Stiller

Mr T J Vincent

ASSESSORS

Mr R Black

Dr M J Quinn

SECRETARIAT

Dr R Hamlet

Dr Nezahat Hunter

Dr C R Muirhead

APPENDIX C

DECLARATION OF MEMBERS' INTERESTS CODE OF PRACTICE

Introduction

1 This code of practice guides members of COMARE as to the circumstances in which they should declare an interest in the course of the Committee's work.

2 To avoid any public concern that commercial interests of members might affect their advice to Government, Ministers have decided that information on significant and relevant interests of members of its advisory committees should be on the public record. The advice of the Committee frequently relates to matters which are connected with the nuclear industry generally and, less frequently, to commercial interests involving radioactivity and it is therefore desirable that members should comply with the Code of Practice which is set out below.

Scope and definitions

3 This code applies to members of COMARE and sub-groups or working groups of COMARE which may be formed.

4 For the purposes of this Code of Practice, the 'radiation industry' means:

(a) companies, partnerships or individuals who are involved with the manufacture, sale or supply of products processes or services which are the subject of the Committee's business. This will include nuclear power generation, the nuclear fuel reprocessing industry and associated isotope producing industries, both military and civil;

(b) trade associations representing companies involved with such products;

(c) companies, partnerships or individuals who are directly concerned with research or development in related areas;

(d) interest groups or environmental organisations with a known interest in radiation matters.

It is recognised that an interest in a particular company or group may, because of the course of the Committee's work, become relevant when the member had no prior expectation this would be the case. In such cases, the member should declare that interest to the Chairman of the meeting and thereafter to the Secretariat.

5 In this code, 'the Department' means the Department of Health, and 'the Secretariat' means the secretariat of COMARE.

Different types of interest – definitions

6 The following is intended as a guide to the kinds of interests which should be declared. Where a member is uncertain as to whether an interest should be declared he or she should seek guidance from the Secretariat or, where it may concern a particular subject which is to be considered at a meeting, from the Chairman at that meeting. Neither members nor the Department are under an obligation to search out links between one company

and another, for example where a company with which a member is connected has a relevant interest of which the member is not aware and could not reasonably be expected to be aware.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them to the Secretariat in writing and to the Chairman at the time the issue arises at a meeting.

Personal interests

6.1 A personal interest involves payment to the member personally. The main examples are:

(a) Consultancies or employment: any consultancy, directorship, position in or work for the radiation industries which attracts regular or occasional payments in cash or kind.

(b) Fee-paid work: any work commissioned by those industries for which the member is paid in cash or kind.

(c) Shareholdings: any shareholding in or other beneficial interest in shares of those industries. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

Non-personal interests

6.2 A non-personal interest involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:

(a) Fellowships: the holding of a fellowship endowed by the radiation industry.

(b) Support by industry: any payment, other support or sponsorship by the radiation industry which does not convey any pecuniary or material benefit to a member personally but which does benefit their position or department, eg:

(i) a grant from a company for the running of a unit or department for which a member is responsible;

(ii) a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students, but does include work carried out by postgraduate students and non-scientific staff, including administrative and general support staff.

(iii) the commissioning of research or work by, or advice from, staff who work in a unit for which the member is responsible.

(c) Support by charities and charitable consortia: any payment, other support or sponsorship from these sources towards which the radiation industry has made a **specific and readily identifiable** contribution. This does not include unqualified support from the radiation industry towards the generality of the charitable resource.

Trusteeships: where a member is trustee of a fund with investments in the radiation industry, the member may wish to consult the Secretariat about the form of declaration which would be appropriate.

Members are under no obligation to seek out knowledge of work done for or on behalf of the radiation industry within departments for which they are responsible if they would not reasonably expect to be informed.

Declaration of interests

Declaration of interests to the department

7 Members should inform the Department in writing when they are appointed of their current personal and non-personal interests and annually in response to a Secretariat request. Only the name of the company (or other body) and the nature of the interest is required; the amount of any salary, fees, share-holding, grant, etc, need not be disclosed to the Department. An interest is current if the member has a continuing financial involvement with the industry, eg if he or she holds shares in a radiation company, has a consultancy contract, or if the member or the department for which he or she is responsible is in the process of carrying out work for the radiation industry. Members are asked to inform the Department at the time of any change in their personal interests, and will be invited to complete a form of declaration once a year. It would be sufficient if changes in non-personal interests are reported at the next annual declaration following the change. (Non-personal interests involving less than £1000 from a particular company in the previous year need not be declared to the Department.)

Declaration of interests at meetings and participation by members

8 Members are required to declare relevant interests at Committee meetings and to state whether they are personal or non personal interests. The declaration should include an indication of the nature of the interest.

(a) If a member has a current (personal or non-personal) interest in the business under discussion, he or she will not automatically be debarred from contributing to the discussion subject to the Chairman's discretion. The Chairman will consider the nature of the business under discussion and of the interest declared (including whether it is personal or non-personal) in deciding whether it would be appropriate for the relevant member to participate in the item.

(b) If a member has an interest which is not current in the business under discussion, this need not be declared unless not to do so might be seen as concealing a relevant interest. The intention should always be that the Chairman and other members of the Committee are fully aware of relevant circumstances.

9 A member who is in any doubt as to whether he or she has an interest which should be declared, or whether to take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether or not a member with an interest shall take part in the proceedings.

10 If a member is aware that a matter under consideration is or may become a competitor of a product process or service in which the member has a current personal interest, he or she should declare the interest in the company marketing the rival product. The member should seek the Chairman's guidance on whether to take part in the proceedings.

11 If the Chairman should declare a current interest of any kind, he or she should stand down from the chair for that item and the meeting should be conducted by the Deputy Chairman or other nominee if he or she is not there.

12 Some members of the Committee may, at the time of adoption of this note, or (in the case of new members) of their joining the Committee, be bound by the terms of a contract which requires them to keep the fact of the contractual arrangement confidential. As a transitional measure, any member so affected should seek to agree an entry for the public record (see paragraph 14) with the other party. If such agreement does not prove possible, the members shall seek a waiver permitting them to disclose their interest, in confidence, to the Chairman and the Secretariat. The Secretariat will maintain a confidential register of such disclosures which will not form part of the public record.

13 On adoption of this note members shall not enter into new contractual obligations which would inhibit their ability to declare a relevant interest.

Record of interests

14 A record will be kept in the Department of the names of members who have declared interests to the Department on appointment, as the interest first arises or through an annual declaration, and the nature of the interest.

15 Information from the record will be made available by the Secretariat to bona-fide enquirers and published by any other means as and where the Department deems appropriate.

Members' declarations of interests – 2006

Member	Company	Personal interest	Company	Non-personal interest
Prof F Alexander		None		None
Prof T C Atkinson		None		None
Dr H R Baillie-Johnson		None		None
Prof A Elliott		None		None
Dr C J Gibson		None		None
Prof S V Hodgson		None	CR-UK	Support for research
Dr J Mackay		None		None
Prof P McKinney		None		None
Prof T McMillan		None	Westlakes Research Inst	PhD students and consumables
Prof M D Mason		None		None
Dr C D Mitchell		None		None
Dr M Murphy	International Power	Shares		None
Prof L Parker		None	Westlakes Research Inst	Research project funding
Dr R A Shields		None		None
Prof A M R Taylor		None		None
Prof J Thacker		None		None
Dr J Verne		None		None
Prof R Waters		None		None
Prof E Wright		None		None