Cancer in the Offspring of Female Radiation Workers – a Record Linkage Study

C R Muirhead [a], K J Bunch [b], N Hunter [a], G J Draper [b], G M Kendall [b], J A O'Hagan [a], M A Phillipson [a], T J Vincent [b] and W Zhang [a]

ABSTRACT

This study was undertaken in order to re-assess an earlier finding of an increased risk of childhood cancer among the offspring of UK women radiation workers exposed to ionising radiation before the child's conception. The study involved the collection of new data as well as a pooled analysis of the new and original datasets and used a similar methodology to that in the earlier study. The new data provided no evidence of an association between childhood cancer and maternal preconception radiation work and analysis of the pooled data showed no statistically significant increase in childhood cancer risk. Considering the pooled data, a weak association was found between maternal radiation work during pregnancy and childhood cancer in offspring although the evidence is limited by the small numbers of linked cases and controls. Neither the new nor the pooled data support our earlier suggestion of a raised risk of childhood cancer in the offspring of female radiation workers.

[a] *Health Protection Agency, Radiation Protection Division*
[b] *Childhood Cancer Research Group, University of Oxford*

Centre for Radiation, Chemical and Environmental Hazards
Radiation Protection Division
Chilton, Didcot, Oxfordshire OX11 0RQ

Approval: December 2009
Publication: December 2009
£15.00
ISBN 978-0-85951-656-3

EXECUTIVE SUMMARY

Fathers' radiation exposure at work and cancer in their offspring has been investigated extensively following the publication of the study by Gardner et al (1990a, b) and its associated hypothesis: that radiation exposure at work to fathers was causally associated with the incidence of leukaemia and non-Hodgkin lymphoma in their children. However, cancer in the offspring of female radiation workers has received relatively little attention because women generally form a small proportion of all radiation workers.

We investigated occupational radiation exposures to women and subsequent cancer among their offspring as part of an earlier study in which national databases of childhood cancers and matched controls were linked to a national database of radiation workers. We have now conducted a new study, based on more recent data which include the mothers of 16,964 case children and their 16,964 matched controls. As before, this was a case-control study for which mothers of children who developed cancer and those of matched control children were identified using the National Registry of Childhood Tumours. Record linkage techniques were then used to identify which of these mothers were included on the National Registry for Radiation Workers. The data were analysed using exact methods for conditional logistic regression analysis.

Within the new data, 4 of the mothers of childhood cancer cases had been radiation workers prior to the child's conception, whereas 7 mothers of matched controls had been radiation workers during the same period. When combined with the earlier results, mothers of 52,612 childhood cancer cases and the same number of controls were included in the pooled analysis with 19 case mothers and 10 control mothers were identified as being occupationally exposed before child's conception. Based on pooled analysis of the original and the new datasets we found no statistically significant association between the risk of childhood cancer and maternal radiation work prior to conception (relative risk (RR) 1.90; 95% confidence interval (CI) 0.84-4.58). Risks of childhood cancer were not statistically significantly raised according to whether or not the mother had left employment with an NRRW employer before the date of conception, but the small numbers of linked cases and controls limit interpretation of this finding. We found some suggestion of a raised risk of childhood cancer in the offspring of women who had been radiation workers during the relevant pregnancy (RR 7.00, 95% CI: 0.90-315, P=0.07), although based on small numbers (7 cases and 1 control in the pooled dataset, of which 3 cases and 1 control were in the new data). There were no statistically significant trends in childhood cancer risk with either the mother's radiation dose prior to conception or the radiation dose *in utero*, nor was any particular diagnostic group over-represented in the linked cases.

Overall, the results do not support the suggestions from the earlier study of a raised risk of childhood cancer in the offspring of female radiation workers. Considering the pooled data, a weak association was found between maternal radiation work during pregnancy and childhood cancer in offspring although the evidence is limited by the small numbers of linked cases and controls.

CONTENTS

1 INTRODUCTION

Investigations undertaken during the 1980s established a raised incidence of childhood leukaemia near the Sellafield and Dounreay nuclear installations (Black, 1984; COMARE, 1988). This led to plans to conduct a comprehensive study to test the hypothesis that childhood cancer can be caused by occupational exposure of parents to ionising radiation before the conception of the child. While that study was being planned, Gardner and colleagues (Gardner et al, 1990a,b; Gardner, 1992) reported an association between occupational paternal preconception irradiation (PPI) and the incidence of leukaemia and non-Hodgkin lymphoma (LNHL) in the children of workers at the Sellafield nuclear plant. In the light of those findings, the principal focus of our earlier study (Draper et al, 1997a,b; Sorahan et al, 2003) became a test of the validity of Gardner's findings.

Our earlier study involved linking records from the National Registry for Radiation Workers (NRRW) to relevant records from the National Registry of Childhood Tumours. The aims were to test the 'Gardner hypothesis' at a national level and to investigate whether radiation exposure of either mother or father is a cause of cancer in their children. The results were first published in 1997 (Draper et al, 1997a,b). A later analysis (Sorahan et al, 2003) included improved estimates of radiation doses and also an investigation of whether the results depended on whether the fathers of the children were involved in radiation work at the time of conception of the child (an "employment timing analysis"). After excluding the cases studied by Gardner and colleagues, we found a statistically significantly raised risk of LNHL - but not of other cancers - among the children of male radiation workers. However, there was no evidence of a dose-response relationship. Thus the results of our earlier study did not support Gardner's hypothesis that PPI is a cause of childhood LNHL, nor did we find any evidence of an association between PPI and other categories of childhood cancer.

The reason for the raised incidence, if it is not due to chance, is not certain. There is evidence from various sources (summarised in COMARE 2006, and by McNally and Eden 2004) that childhood leukaemia may in some instances be related to exposure to infection. Kinlen (Kinlen 1988, 1995a, 1997; Kinlen et al 1993) proposed that childhood leukaemia can be a rare response to a common but unidentified infection: excess cases of 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, leading to localised epidemics of the underlying infection. Support for the possible importance of population mixing came from the employment timing analysis of the earlier study (Sorahan et al, 2003). This found that the elevated risk of LNHL was limited to those whose fathers were still radiation workers at conception. Children whose fathers stopped radiation work prior to their conception were found to have no excess risk of LNHL. No increased relative risks were found for other cancers.

Considering the children of women radiation workers, our earlier study showed a statistically significantly raised risk for childhood cancers in general among the children of exposed women radiation workers, although again with no evidence of a dose-response relationship. Moreover, the effect was concentrated in malignancies other

than LNHL and was not confined to any specific childhood cancer diagnostic subgroup. This finding was based on small numbers of linked cases and controls and the increased risk could not be attributed to *in utero* exposure. Because the number of cases was small, no employment timing analysis was carried out for the offspring of female radiation workers.

The current study re-examines the question of whether there is an association between maternal occupational exposure to ionising radiation and childhood cancer in subsequent offspring, by using data additional to those available earlier. In particular, it includes childhood cancer incidence data accrued between 1987 and 1999. Analyses of these more recent data are compared with the findings obtained previously.

A summary article based on this research has been published in the peer-reviewed literature (Bunch et al, 2009).

2 DATA SOURCES

2.1 National Registry of Childhood Tumours (NRCT)

The NRCT is a population-based registry covering England, Wales and Scotland (Stiller, 2007). It includes nearly all children under the age of 15 diagnosed with malignant disease from 1962 onwards, together with most children who died of cancer from 1953 onwards. It is the largest register of childhood cancers in the world, with data on more than 80,000 children. Data from the registry are used extensively by researchers within both the Childhood Cancer Research Group and the wider academic community.

The very high quality and completeness of this database is due largely to the contribution made by many collaborating organisations. The Children's Cancer and Leukaemia Group (CCLG) was formed in 2006 as a merger of the United Kingdom Children's Cancer Study Group (UKCCSG) and the Childhood Leukaemia Working Party. The CCLG is the national organisation for paediatric oncologists and others working in the field of childhood cancer, and its members are responsible for the care of nearly all children presenting with malignant disease in the United Kingdom. The CCLG maintains a register of children under the care of its members and their data centre sends copies of notifications and of information on children entered into trials to the NRCT. For most patients this is the initial source of NRCT ascertainment. Copies of cancer registrations relating to children aged under 15 years are also sent to the NRCT by the Office for National Statistics (ONS), the Information and Statistics Division of the Scottish Health Service (ISD) and the regional cancer registries that cover all age groups. There are also several specialist children's tumour registries in various parts of Britain and these also send copies of notifications received to the NRCT.

Before 1962, death certificates were the principal source of ascertainment of cases. This was adequate for early epidemiological studies, because most children at that time would have died of their cancer. However, survival rates are now so much improved that mortality is not a good indicator of incidence. Although very few cases are now ascertained solely from death certification, copies of death certificates for all deaths occurring before the age of 20 years with a neoplasm coded as the underlying cause are sent to the NRCT by ONS (for England and Wales) and by the General Register Office (GRO(S)) (for Scotland).

2.2 National Registry for Radiation Workers (NRRW)

The NRRW, a study designed to investigate the possibility of increased mortality or incidence of cancer associated with occupational exposure to ionising radiation, was set up in 1975 following discussions between researchers and representatives from the nuclear industry. The study, operated by researchers at the Health Protection Agency's Radiation Protection Division (HPA-RPD) (formerly the National Radiological Protection Board, NRPB), now holds details of over 200,000 male and female workers occupationally exposed to ionising radiation in the UK. The NRRW is the only UK-wide

study for radiation workers both in and outside the nuclear industry (Kendall et al, 1992; Muirhead et al, 1999a,b, 2009).

Data for workers has been added to the NRRW database throughout the period 1976 to the present. Initial efforts concentrated on those workers then still in employment with participating organisations while subsequent effort was directed towards collecting data for workers employed from the late 1940s through to the mid-1970s as well as extending coverage to additional organisations and those workers still joining the participating companies. Inclusion in the NRRW is optional although participation rates are high with a refusal rate of only just over 1% reported in the second and third NRRW analyses (Muirhead et al, 1999a,b, 2009).

In addition to the opportunity to opt-out of the NRRW, information about the current study was passed to employers participating in the NRRW, so that female radiation workers in the NRRW would have the opportunity to opt-out of this study. As mentioned in section 3.2 below, the level of opt-out was very low. Updates on progress with the study were provided via periodic NRRW newsletters and through links with the NRRW Steering Group. Furthermore, briefings were given to management and workforces, both at the start of the study and shortly before publication of the findings by Bunch et al (2009).

Most of the workers participating in the NRRW have been employed by major nuclear industry employers such as BNFL (British Nuclear Fuels), UKAEA (UK Atomic Energy Authority), AWE (Atomic Weapons Establishment) or the power supply companies but the Ministry of Defence (MOD) is also a large contributor. Other groups of employees, such as those at research organisations (eg. workers at the Daresbury and Rutherford Laboratories of the STFC – the Science and Technology Facilities Council) and commercial companies (eg. Rolls Royce Submarines or GE Healthcare), are also included in the study.

The NRRW uses a simple 'industrial/non-industrial' classification in order to allow for effects of social class on health. This classification is widely utilised in the nuclear industry and broadly corresponds to a distinction between weekly and monthly paid staff. It correlates well with social class, industrial corresponding to V, IV and III (manual) and non-industrial to III (non-manual), II and I (Duncan and Howell, 1970; Muirhead et al, 1999b).

To date, three analyses of the NRRW have been reported (Kendall et al, 1992; Muirhead et al, 1999a,b, 2009). The most recent analysis was based on a study population of just under 175,000 male and female workers (Muirhead et al, 2009).

NRRW data collection

Personal and dose data on workers are supplied to the NRRW by the participating organisations. These data include the following:-

- Identifying information such as name, date of birth, sex, National Insurance Number and National Health Service Number.
- Information on employment history such as start and stop dates and industrial classification.

- Radiation dose history, based on annual recorded exposures to external radiation, with, as a minimum, indicators as to whether the worker had been monitored for internal contamination. External doses are assessed using film badges, thermoluminescent detectors or electronic personal dosemeters worn by the workers (Britcher et al, 1991), whereas monitoring for internal exposure is based on measurements of radionuclide concentrations in, for example, urine (Riddell et al, 2000).

3 METHODS

To assess the possible risks from maternal radiation exposure, we needed first to identify cases of childhood cancer diagnosed in the relevant period and to assemble a set of matched controls. Record linkage could then be used to ascertain which of the mothers of these case and control children had been occupationally exposed to ionising radiation before the child's conception or during the relevant pregnancy.

3.1 Identification of childhood cancer cases and controls

Cases of childhood cancer (diagnosed before the child's fifteenth birthday) were identified from the NRCT. Children had been eligible for our earlier study (Draper et al, 1997a, b) if they had been born and diagnosed in Britain between 1952 and 1986. The current study additionally includes all British-born children diagnosed in Britain from 1987 up to the end of 1999; some of these children were therefore born before 1987. Ascertainment is considered virtually complete for leukaemia for this period and only marginally less so for other diagnostic groups.

For each case child, the ONS was asked to locate the child's birth registration entry and select a control from the same birth register, matched on sex and born within 6 months of the case. For both case and control children, ONS returned birth registration details to the study investigators, including child's place of birth, mother's address at the time of birth, and the names, places of birth and - where recorded - occupations of the child's parents. Maternal occupation as recorded at time of birth was not used to identify children of women radiation workers *per se* but was of value in validating possible matches during the record linkage process (see section 3.3). Parental dates of birth are held by ONS on the confidential part of the birth record and could not be supplied. For children born in Scotland, the corresponding information for both cases and controls was obtained from GRO(S).

Of the NRCT cases for the relevant period, 2.2% were born abroad or adopted and a further 4.5% could not be traced at ONS/GRO(S). However, birth registration details were returned for the remaining 93% (see Appendix A1). The record linkage that followed included the mothers of 16,964 case children and of 16,964 matched controls.

3.2 Identification of females in the National Registry for Radiation Workers (NRRW)

Worker records

As mentioned in section 2.2, NRRW women participants were made aware of their option to withdraw from the study and 9 women chose to be excluded. The remaining 15,840 female workers were included in the cohort to be linked to the case and control mothers described above. The women included in the cohort had been employed, as radiation workers, by NRRW participating organisations at any time before 1st January

2000. The tables in Appendix A2 show more details relating to the women workers included in this current study.

In comparison to the earlier linkage study, data for an extra 4200 female radiation workers were available. This reflects extensions of the NRRW cohort with both those radiation workers joining the participating organisations in more recent years, as well as the addition of extra groups of earlier workers whose records were not available at the time of the previous study. Particular groups of workers for whom older records have now become available include those employed at BNFL Capenhurst and BNFL Springfields before 1976, those employed by the Ministry of Defence before 1977 and those workers employed at GE Healthcare (formerly Amersham International) between 1976 and 1981.

Dosimetry data and dose corrections for this study

As noted above, radiation doses are stored on the NRRW as annual totals. Additionally, in some instances, there are lifetime components of dose before the start of an NRRW employment that have not been subdivided into annual totals.

For the purposes of this study, in order to estimate doses before and around the time of conception or birth, doses were required for periods shorter than a year. Therefore, for those workers identified as mothers of childhood cancer cases or controls, the following information was sought from organisations participating in the NRRW**.**

(i) For calendar years shortly before and after the child's conception or birth, the results of individual dosemeter assessments of external whole body doses as well as, in the years for which a record exists, the annual whole body doses. Doses were generally determined using film badges, thermoluminescent dosimeters (TLDs) or electronic personal dosemeters. These were typically issued for periods of a month, although shorter periods were not uncommon and longer periods were sometimes used, particularly for TLDs.

(ii) The appropriate transfer records of doses, if doses had been received in a different employment. A transfer record is a document issued by an employer to a radiation worker who leaves employment, so as to inform the individual and any future employer of the doses that he or she has received. Transfer records are discussed in more detail in NRRW reports (Kendall et al, 1992; Muirhead et al, 1999b).

(iii) Information about exposures from internal emitters during the above period, together with corresponding details for earlier years. The degree of information available as to which radionuclides were monitored for, the periods of monitoring and measured levels of contamination, was variable across organisations and time. As a minimum, organisations were able to state which women had been monitored for potential internal exposures prior to conception.

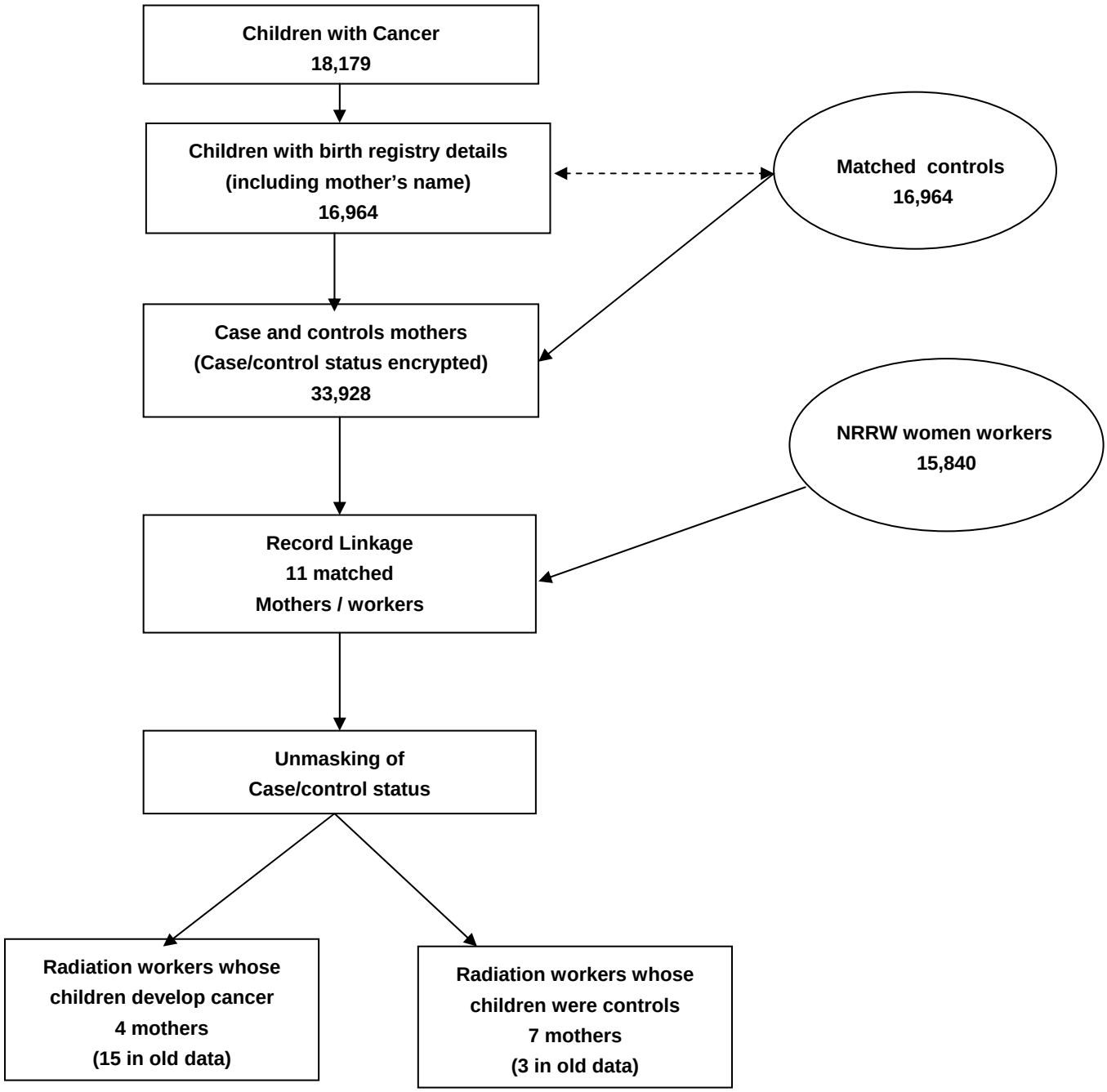
It has been recorded elsewhere (Muirhead et al, 1999b) that programmes of personal monitoring were, over much of the period considered, primarily designed to demonstrate that legal or administrative limits on individual doses were observed. For this reason, conventions were sometimes adopted which introduced biases into the dose records. For this study, corrections were therefore applied to the recorded doses so as to remove

or minimise these biases. Full details of such corrections can be found elsewhere (Muirhead et al, 1999b). For workers included in the Nuclear Industry Combined Epidemiological Analysis (NICEA) study, more refined estimates of dose were made (Carpenter et al, 1994). The original data cited in this report are based on the corrected doses described by Sorahan et al (2003), and differ slightly from the values given by Draper et al (1997a,b) which did not include these refined dose estimates for workers in the NICEA study.

3.3 Record linkage methodology

Computerised record linkage was used to compare the names of the mothers of cases and controls in the study with those of the women radiation workers on the NRRW. The method used was based on the Generalised Iterative Record Linkage System (Howe, 1985), developed at the National Cancer Institute of Canada and modified for the present study. Pairs of records (one relating to a case or control mother and the other an NRRW woman worker) were compared if the New York State Intelligence Information System (NYSIIS) codes, as modified for the UK, derived from their surnames were identical. Consideration of such pairs of records has been shown to bring together genuinely matching records in some 98% of cases (Newcombe, 1988). Records were considered for possible linkage by assigning a composite score, derived by summing individual scores resulting from separate comparisons of surnames and forenames. The comparisons take into account the overall frequency of the values for each item: consequently, the concurrence of more commonly occurring names resulted in lower scores than those of less common names. Pairs of records with a composite score above a pre-set level were then scrutinised, using any further available supplementary information, to decide whether it was reasonable to conclude that the two records related to the same woman. The schematic illustration in Figure 1 summarises the record linkage technique.

Figure 1: Process of record linkage



The following series of checks were applied, in order to identify conflicting information and permit many possible outstanding links to be refuted.

1. A detailed examination of names was made. Where clear conflicts were evident, beyond the level identified by the linkage program, potential matches were excluded.

2. The worker's and the mother's alternative names were compared and contradictory information resulted in potential matches being excluded. It should be noted that while it is a legal requirement for the mother to declare her present and all previous surnames on registering a child's birth, the NRRW would not necessarily record surnames used at times other than while the mother was employed at one of the participating organisations.

3. The worker's employment details and the mother's occupation, if recorded, at the child's birth registration, were compared. Where there was clear conflict, the potential match was excluded.

4. The worker's employment details and the child's place of birth, as recorded at their birth registration, were compared. Where employment information included a specific location at the time of the child's birth, the potential match could be excluded if the employment location conflicted with the child's place of birth.

5. For matches that were still considered possible (i.e. after the above checks), we obtained from ONS the worker's place of birth, as recorded in her own birth registration details. This was then compared with the mother's place of birth as recorded at the child's registration; where the two were in clear conflict, the potential match was excluded.

6. For mothers who were married to the child's father at the time of the child's birth, we requested copies of the marriage certificate from ONS. This gave us the mother's age at the time of marriage and where this was incompatible with the worker's date of birth the potential match was excluded.

7. For matches that were still feasible on the basis of mother's age at marriage, we requested the mother's own birth registration details from ONS. This enabled us to exclude potential matches where the mother's and worker's dates of birth did not agree.

For registrations - either the child's or the mother's - that took place in Scotland, similar procedures to those above were undertaken but the registration information was sought from GRO(S) rather than ONS.

At this stage in the validation process, there were some matches that were still deemed possible but for which it had not been possible to obtain the mother's date of birth to confirm the link, either because ONS/GRO(S) had been unable trace the necessary information or because the mother was unmarried at the time of the child's birth. For such matches we attempted to obtain the mother's date of birth, by contacting the child's general practitioner (GP). We wrote to GPs, explaining the study and the ethical approval it had received, gave them the possibly matched worker's date of birth and

asked them to confirm whether this was the mother's date of birth. Finally, by careful examination of all available information, we were able to conclude that the workers' and mothers' records involved in the very small number of unresolved matches related to different women.

The record linkage process was undertaken entirely blind to the case/control status of the mothers involved, in order to avoid any introduction of bias. Only when the definitive set of linked records had been agreed was the case/control status of these records revealed.

3.4 Statistical methods

Statistical analysis involved the calculation of relative risks (RRs) to measure the association between maternal radiation exposure and the risk of childhood cancer – either taken as a whole or for specific types of cancer – for the offspring of various groups of workers as compared with the unexposed female population. Four maternal preconception dose categories and four *in utero* exposure categories were studied: these are same as those used previously (Draper et al, 1997a,b; Sorahan et al 2003), namely:

- <0.1 mSv, 0.1-4.9 mSv, 5.0-49.9 mSv and $\geq$ 50.0 mSv for total preconception dose, and
- <0.1 mSv, 0.1-0.9 mSv, 1.0-1.9 mSv and $\geq$ 2 mSv for *in utero* dose.

Data were analysed for all childhood cancers combined and separately for two major categories of childhood cancers: leukaemia and non-Hodgkin lymphoma (NHL) combined and the grouping of all other childhood cancers.

Relative risks of cancer in offspring were also estimated comparing female workers monitored for internal radiation exposure with other female radiation workers and comparing industrial and non-industrial female radiation workers. Further analyses were performed to examine potential differences in cancer risk among offspring according to the timing of the mother's employment at an NRRW participating facility relative to child's conception and cancer diagnosis.

Exact methods of inference for conditional logistic regression analysis of matched case-control data were used to derive relative risks and 95% Confidence Intervals (CIs), using the LogXact statistical computer package (LogXact, 2005). This analytical technique is important because standard asymptotic likelihood-based inference may produce inaccurate P-values and confidence intervals - and sometimes may be unable to produce any estimates for small, sparse and unbalanced datasets (Mehta and Patel, 1995). Appendix B gives a more detailed description of exact methods for logistic regression.

All the statistical tests were two-sided and P values < 0.05 were taken as statistically significant. Categorical variables were analysed by assigning indicators for each category in the model. Tests for trend in risk with radiation dose treated as a continuous variable were carried out using exact methods. In this instance, we calculated deviance

statistics to assess the evidence for including radiation and other variables in the modelled relative risk, as compared to the null model (see details in Appendix B). Tests for differences between the relative risks in the new and the original data were performed using a chi-squared test.

4 RESULTS

In total, information on the mothers of 52,612 childhood cancer cases and the same number of controls was included in the pooled analysis. Of these, the mothers of 16,964 cases and 16,964 controls were from the new dataset and – amongst these - the mothers of 4 cases and 7 controls were identified from the NRRW as being occupationally exposed prior to the child's conception. In total, there were 19 case mothers and 10 control mothers identified as being occupationally exposed in the pooled data.

Table 1 gives the results of categorical analyses for maternal preconception dose and *in utero* dose. Throughout the Tables, results are presented by cancer type and separately for the original data, the new data (highlighted in grey), and the pooled data. Table 2 presents analogous analyses for status of exposure to internal emitters (monitored/not monitored) and industrial classification (industrial/non industrial). Table 3 presents the results of analysis of deviance for logistic regression models relating childhood cancer risks to radiation worker status and maternal dose considered as a continuous variable. Table 4 gives the results of further analyses to examine potential differences in cancer risk among offspring according to exposure period of the mother.

Most of the relative risks for the new data shown in Tables 1-4 are less than unity, and all of the confidence intervals include unity. Overall, the new data provide no evidence of an association between childhood cancer and maternal preconception radiation work. However, in the original data there was a statistically significantly increased relative risk for all childhood cancers other than leukaemia and NHL (5.50, 95% CI: 1.20 to 51.02) and for all childhood cancers combined (5.00, 95% CI: 1.42 to 26.94) (see Tables 1 and 2). For the latter group, the relative risks estimated for the new and original data were significantly different (chi-square=4.75; P=0.03).

When the new and original data were pooled there was no statistically significant increase for these cancer types (see Tables 1 and 2). In particular, the relative risk of all childhood cancers combined among the offspring of female radiation workers taken as a whole was 1.90 (95% CI: 0.84 to 4.58), based on 19 cases and 10 controls.

Among the group of children with an *in utero* dose due to maternal radiation work, there were no statistically significantly raised risks of leukaemia and NHL, other childhood cancers or all childhood cancers combined in either the new or the original data taken alone (see Tables 1 and 2). There was no statistically significant difference in risks between the new and the original data when analysing *in utero* exposure for all childhood cancers combined. When the new and the original data were pooled there was some indication of a raised risk of all childhood cancers combined (RR 7.00, 95% CI: 0.90 to 315; P=0.07, based on 7 cases and 1 control among the offspring of female

radiation workers), a tendency found in both the old and new studies, though the numbers were very small (case/control ratios 4:0 and 3:1 respectively) (Table 1). There was no evidence of any associations between the level of *in utero* dose and risk but such associations would be hard to detect, given small numbers involved.

Further analyses were performed to assess risks in relation to type of radiation work and the results were given in Table 2. Relative risks among the offspring of female workers monitored for internal exposure – when compared with the offspring of non-radiation workers or with the offspring of radiation workers not monitored for internal exposure - were all consistent with 1 for the original, the new and the pooled data. There were no statistically significant differences in risk between the offspring of industrial and non-industrial workers, or between either of these groups and the offspring of female non-radiation workers for the new, the original and the pooled data, although the numbers were very small.

The results of analysis of deviance for logistic regression models relating childhood cancer risks to radiation worker status and maternal dose considered as a continuous variable are summarised in Table 3. Tests of statistical significance based on deviance statistics and exact P-values are given in the table (see Appendix B, section B2 for details of the methods). In line with the results in Table 2 referred to earlier, maternal radiation work was associated with a highly statistically significant raised risk of all cancers combined in the original data (P=0.004), However, among the offspring of female radiation workers, there was no evidence of a trend in risk with either preconception or *in utero* dose in the original data for any of the diagnostic categories; this can be seen by comparing the fits of a model that includes both preconception dose, D, and whether the worker was linked to the NRRW, L (ie. model D+L) with L alone and of a model that includes both *in utero* dose, DU, and linkage status, L, (ie. model DU+L) with L alone in Table 3 (P>0.10 in all instances). Both in the new and the pooled data, none of the tests for differences or dose trends yielded statistically significant results for any of the diagnostic categories. For 'All cancers other than leukaemia and NHL' in the pooled data, there was borderline evidence of a raised risk in the offspring of radiation workers when compared with other children (P=0.06), but, after allowing for this overall increase, there was no evidence of a trend in risk with either preconception or *in utero* dose (ie. based on comparing the fits of D+L and L or of DU+L and L in Table 3).

Further analyses were also performed to examine potential differences in cancer risk among offspring according to the exposure period: ie. whether the mother left employment at an NRRW-participating facility before the date of conception of the child and had no subsequent employment known to the NRRW; whether the mother was employed at an NRRW-participating facility on the date of the child's conception or subsequently resumed employment at an NRRW participating facility; or whether she was employed in the year of the child's diagnosis (or the corresponding date if the child was a control) (Table 4). In the new data, the relative risks were not statistically significantly raised for any of the exposure periods of maternal employment and for none of the diagnostic categories. However, in the original data, raised risks of childhood cancers were highest among children whose mothers left employment before the child's conception and – for the grouping of all childhood cancers combined - these findings were statistically significant, although the confidence intervals were very wide owing to

the small numbers of subjects (RR=5.50, 95% CI: 1.20, 51, for all cancers combined). For all childhood cancers combined, the risk among the offspring of mothers who left employment before the child's conception was not statistically significantly raised compared to the offspring of non-radiation workers when the new and the original data were pooled. However, as indicated above, there was statistically significant heterogeneity in this relative risk between the new and the original data ($P<0.01$). As with the new data, children whose mothers were employed either on the date of their conception (or subsequently) or in the year of their diagnosis did not have a statistically significantly raised cancer risk in the original data; this was also true for the pooled data.

Table 1: Relative risks for childhood cancer by mother's radiation dose before child's conception and while pregnant

		Original data [d]			New data			Pooled data		
	Dose Group (mSv)	No of Cases	No of Controls	Relative Risk (95% CI) [a]	No of Cases	No of Controls	Relative Risk (95% CI) [a]	No of Cases	No of Controls	Relative Risk (95% CI) [a]
Leukaemia & NHL										
Non-radiation worker [b]		13,855	13,858	1.0	6,206	6,204	1.0	20,061	20,062	1.0
Total pre-conception dose										
	<0.1 [j]	0	0	_	0	0	_	0	0	_
	0.1-4.9	3	1	3.00 (0.24, 157)	1	3	0.33 (0.01, 4.2)	4	4	1.00 (0.19, 5.37)
	5.0-49.9	0	0	-	1	1	1.00 (0.01, 79)	1	1	1.00 (0.01, 79)
	50.0+	1	0	1.00 (0.03, Inf) [c]	0	0	_	1	0	1.00 (0.03, Inf) [c]
All pre-conception dose levels combined		4	1	4.00 (0.40, 197)	2	4	0.50 (0.04, 3.49)	6	5	1.20 (0.31, 4.97)
Radiation worker, no *in utero* employment		4	1	4.00 (0.40, 197)	0	3	0.26 (0, 2.42) [c]	4	4	1.00 (0.19, 5.37)
Radiation worker, *in utero* dose [e]	<0.1 [j]	0	0	_	0	0	_	0	0	_
	0.1-0.9	0	0	_	2	1	2.00 (0.1, 118)	2	1	2.00 (0.10, 118)
	1.0-1.9	0	0	_	0	0	_	0	0	_
	2.0+	0	0	_	0	0	_	0	0	_
All *in utero* dose levels combined		0	0	_	2	1	2.00 (0.1, 118)	2	1	2.00 (0.10, 118)

Table 1 Continued

All cancers excluding leukaemia & NHL										
Non-radiation worker [b]		21,778	21,787	1.0	10,754	10,753	1.0	32,532	32,540	1.0
Total pre-conception										
	<0.1 [j]	2	0	2.41 (0.19, Inf) [c]	0	0	-	2	0	2.41 (0.19, Inf) [c]
	0.1-4.9	5	1	5.00 (0.56, 237)	2	3	0.67 (0.06, 5.82)	7	4	1.75 (0.44, 8.15)
	5.0-49.9	2	1	2.00 (0.1, 118)	0	0	-	2	1	2.00 (0.10, 118)
	50.0+	2	0	2.41 (0.19, Inf) [c]	0	0	-	2	0	2.41 (0.19, Inf) [c]
All pre-conception levels combined		11	2	5.50 (1.20, 51) [h]	2	3	0.67 (0.06, 5.82)	13	5	2.60 (0.87, 9.32)
Radiation worker, no *in utero* employment		7	2	3.50 (0.67, 35)	1	3	0.33 (0.01, 4.15)	8	5	1.60 (0.46, 6.22)
Radiation worker, *in utero* dose [e]										
	<0.1 [j]	2	0	2.41 (0.19, Inf) [c]	0	0	-	2	0	2.41 (0.19, Inf) [c]
	0.1-0.9	1	0	1.00 (0.03, Inf) [c]	1	0	1.00 (0.03, Inf) [c]	2	0	2.41 (0.19, Inf) [c]
	1.0-1.9	0	0	-	0	0	-	0	0	–
	2.0+	1	0	1.00 (0.03, Inf) [c]	0	0	-	1	0	1.00 (0.03, Inf) [c]
All *in utero* dose levels combined		4	0	5.29 (0.66, Inf) [c]	1	0	1.00 (0.03, Inf) [c]	5	0	6.73 (0.92, Inf) [c,f]

Table 1 Continued

All childhood cancers										
Non-radiation worker [b]		35,633	35,645	1.0	16,960	16,957	1.0	52,593	52,602	1.0
Total pre-conception dose										
	<0.1 [j]	2	0	2.41 (0.19, Inf) [c]	0	0	_	2	0	2.41 (0.19, Inf) [c]
	0.1-4.9	8	2	4.00 (0.80, 37)	3	6	0.50 (0.08, 2.34)	11	8	1.38 (0.50, 3.94)
	5.0-49.9	2	1	2.00 (0.10, 118)	1	1	1.00 (0.01, 79)	3	2	1.50 (0.17, 18)
	50.0+	3	0	3.85 (0.41, Inf) [c]	0	0	_	3	0	3.85 (0.41, Inf) [c]
All pre-conception dose levels combined		15	3	5.00 (1.42, 27) [h]	4	7	0.57 (0.12, 2.25)	19	10	1.90 (0.84, 4.58)
Radiation worker, no *in utero* employment		11	3	3.67 (0.97, 20)	1	6	0.17 (0.004, 1.37)	12	9	1.33 (0.52, 3.58)
Radiation worker, *in utero* dose [e]	<0.1 [j]	2	0	2.41 (0.19, Inf) [c]	0	0	_	2	0	2.41 (0.19, Inf) [c]
	0.1-0.9	1	0	1.00 (0.03, Inf) [c]	3	1	3.00 (0.24, 157)	4	1	4.00 (0.40, 197)
	1.0-1.9	0	0	-	0	0	_	0	0	_
	2.0+	1	0	1.00 (0.03, Inf) [c]	0	0	_	1	0	1.00 (0.03, Inf) [c]
All *in utero* dose levels combined		4	0	5.29 (0.66, Inf) [c]	3	1	3.00 (0.24, 157)	7	1	7.00 (0.90, 315) [g]

[a]: Exact 95% CI, calculated using LogXact (2005);
[b]: Not known to have been monitored for occupational exposure before the conception of the survey child. All relative risks are calculated using this as the reference group;
[c]: Conditional maximum-likelihood estimate is not available because the sufficient statistic is at one extreme of its range. The median unbiased point estimate shown with 95% confidence interval (CI);
[d]: Using the corrected doses described by Sorahan et al (2003), which superseded the values reported by Draper et al (1997a,b);
[e]: *In utero* doses were obtained only for women who were monitored before conception;
[j]: Includes monitored workers whose dose, after correction, is zero (see footnote d)
[f]: P=0.06;
[g]: P=0.07;
[h]: P< 0.05.

Table 2: Relative risks for childhood cancer, by type of maternal radiation work

	Original data			New data			Pooled data		
	No of Cases	No of Controls	Relative Risk (95% CI) [a]	No of Cases	No of Controls	Relative Risk (95% CI) [a]	No of Cases	No of Controls	Relative Risk (95% CI) [a]
Leukaemia & NHL									
Radiation worker									
No	13,855	13,858	1.0	6,206	6,204	1.0	20,061	20,062	1.0
Yes	4	1	4.00 (0.4, 197)	2	4	0.50 (0.04, 3.49)	6	5	1.20 (0.31, 4.97)
Monitored for internal exposure									
Radiation worker, not monitored [b]	4	1	4.00 (0.4, 197)	0	4	0.19 (0.0, 1.52) [c]	4	5	0.80 (0.16, 3.72)
Radiation worker, monitored [b]	0	0	_	2	0	2.41 (0.19, Inf) [c]	2	0	2.41 (0.19, Inf) [c]
Radiation worker, monitored vs non monitored [b]			_			8.69 (0.51, Inf) [c]			2.29 (0.16, Inf) [c]
Industrial classification									
Radiation worker industrial/other	0	0	_	0	1	1.00 (0.0, 39) [c]	0	1	1.00 (0.0, 39) [c]
Radiation worker, non industrial	4	1	4.00 (0.4, 197)	2	2	1.00 (0.07, 14)	6	3	2.00 (0.43, 12)
Unknown	_	_	_	0	1	1.00 (0.0, 39) [c]	0	1	1.00 (0.0, 39) [c]
Radiation worker, industrial vs non-industrial			_			1.50 (0.0, 59) [c]			0.67 (0.0, 26) [c]

All cancers excluding leukaemia & NHL									
Radiation worker									
No	21,778	21,787	1.0	10,754	10,753	1.0	32,532	32,540	1.0
Yes	11	2	5.50 (1.20, 51) [e]	2	3	0.67 (0.06, 5.82)	13	5	2.60 (0.87, 9.32)
Monitored for internal exposure									
Radiation worker, not monitored [b]	11	1	11.0 (1.60, 473) [e]	1	2	0.50 (0.008, 9.60)	12	3	4.0 (1.08, 22) [e]
Radiation worker, monitored [b]	0	1	1.00 (0.00, 39) [c]	1	1	1.00 (0.01, 79)	1	2	0.50 (0.01, 9.60)
Radiation worker, monitored vs not-monitored [b]			0.18 (0.0, 7.09) [c]			1.73 (0.01, 234)			0.14 (0.002, 3.63)
Industrial classification									
Radiation worker industrial/other	4	2	2.00 (0.29, 22)	1	1	1.00 (0.01, 79)	5	3	1.67 (0.32, 11)
Radiation worker, non industrial	7	0	9.61 (1.44, Inf) [e] [c]	1	2	0.50 (0.01, 9.60)	8	2	4.00 (0.80, 37)
Radiation worker, industrial vs non-industrial			0.31 (0.0, 4.37) [c]			1.73 (0.01, 234)			0.92 (0.03, 5.32)
All childhood cancers									
Radiation worker									
No	35,633	35,645	1.0	16,960	16,957	1.0	52,593	52,602	1.0
Yes	15	3	5.00 (1.42, 27) [e]	4	7	0.57 (0.12, 2.25)	19	10	1.90 (0.84, 4.58)
Monitored for internal exposure									
Radiation worker, not monitored [b]	15	2	7.50 (1.74, 68) [e]	1	6	0.17 (0.004, 1.37)	16	8	2.00 (0.81, 5.40)
Radiation worker, monitored [b]	0	1	1.00 (0.00, 39) [c]	3	1	3.00 (0.24, 157)	3	2	1.50 (0.17, 18)
Radiation worker, monitored vs not-monitored [b]			0.20 (0.0, 7.80) [c]			12.00 (0.50, 1097)			0.76 (0.07, 11)
Industrial classification									
Radiation worker industrial/other	4	2	2.00 (0.29, 22)	1	2	0.50 (0.008, 9.60)	5	4	1.25 (0.27, 6.30)
Radiation worker, non industrial	11	1	11.00 (1.60, 473) [e]	3	4	0.75 (0.11, 4.43)	14	5	2.80 (0.95, 9.93) [d]
Unknown	_	_	_	0	1	1.00 (0.0, 39) [c]	0	1	1.00 (0.0, 39) [c]
Radiation worker, industrial vs non-industrial			0.20 (0.003, 4.88)			0.69 (0.01, 20))			0.37 (0.05, 2.82)

[a]: Exact 95% CI, calculated using LogXact (2005);
[b]: Monitoring status refers to internal radiation exposure. All of these radiation workers were monitored for external exposure;
[c]: Conditional maximum likelihood estimate is not available because the sufficient statistic is at one extreme of its range. The median unbiased point estimate is shown with 95% confidence interval (CI);
[d]: P=0.06; [e]: P<0.05.

Table 3: Decreases in deviance (DEV) and in the number of fitted parameters (DF) with respect to the null model associated with exact conditional logistic regression fits of maternal dose variables, using an exponential model

		Original data		New data		Pooled data	
Model	DF	DEV	P	DEV	P	DEV	P
Leukaemia & NHL							
D	1	3.09	>0.10	0.09	>0.10	1.22	>0.10
L	1	1.93	>0.10	0.68	>0.10	0.09	>0.10
D+L	2	4.16	>0.10	0.83	>0.10	1.26	>0.10
DU	1	0.00	>0.10	0.01	>0.10	0.01	>0.10
DU+L	2	0.00	>0.10	1.07	>0.10	0.16	>0.10
All cancers excluding leukaemia & NHL							
D	1	2.48	>0.10	2.05	>0.10	2.18	>0.10
L	1	6.86	0.01	0.20	>0.10	3.68	0.06
D+L	2	6.94	0.06	3.08	>0.10	4.16	>0.10
DU	1	2.77	>0.10	1.39	>0.10	4.16	>0.10
DU+L	2	7.59	0.02	2.43	>0.10	5.86	0.05
All childhood cancers							
D	1	3.99	0.10	0.60	>0.10	3.39	>0.10
L	1	8.73	0.004	0.83	>0.10	2.84	>0.10
D+L	2	9.09	0.02	0.88	>0.10	4.34	>0.10
DU	1	2.77	>0.10	0.57	>0.10	2.31	>0.10
DU+L	2	9.51	0.01	3.11	>0.10	3.89	>0.10

P: Exact P-value.

D: Total corrected preconception dose (continuous variable).

L : Radiation worker (radiation dose recorded with the NRRW before conception of the survey child) (categorical variable: yes; no).

DU: Total corrected *in utero* dose (continuous variable).

D+L: Indicates that both D and L are included in the regression analysis.

5 DISCUSSION

5.1 Study characteristics

This study is based entirely on data from existing registers and is thus free of bias arising from the selection of cases and controls or as a result of differential response rates. In line with current legislation and good practice, women radiation workers were advised of their right to withdraw from the study, but only 9 out of 15,840 chose to do so. The great majority of UK radiation workers in the nuclear industry are included in the NRRW, as are a good proportion of radiation workers employed elsewhere in the UK (with the exception of those in the medical field). Although these employees have historically been predominately male, a significant minority of exposed employees have been female. Many of these female employees have been occupationally exposed for only short periods of time, and an advantage of our study design is that all employees, regardless of the length of time for which they were exposed, contribute to the analysis.

No formal calculations to predict the number of matches were possible because there is no reliable information available about the childbearing patterns of female radiation workers and it cannot be assumed that these patterns are the same as those for the female population as a whole. Because of the importance of identifying every mother, whether of a case or control child, who was an NRRW member, great attention was paid to every possible match in carrying out the record linkage procedures and potential matches were only excluded on the basis of additional conflicting information. The researchers involved with decisions to confirm or exclude possible matches and also those obtaining detailed dosimetry information were blind to the case/control status of the possible matches. Thus if any genuine matches were not identified, they were equally likely to have involved the mothers of case or control children. There is no doubt that the linkage would have been simpler and less time consuming if information on the mother's date of birth were available from the child's birth registration details but there is a legally binding embargo on this extra information. However, despite these problems, we feel that the record linkage procedures were successful in identifying case and control mothers within the NRRW.

The cases included in the new dataset were selected according to the same criteria as those for the original study. Changing social patterns within the UK, in particular the increased frequency in more recent years of children being registered under a surname different from that of both their parents or of subsequently changing their surname to reflect family changes may have contributed to the higher rate of untraced children's birth records at ONS/GRO(S) in the new data. Changing patterns of immigration may also have affected the numbers of children for whom a birth record could not be traced because they were born abroad. However, these changes are very unlikely to have affected the results of the study. Although there is no clear boundary to the timing of exposure for the matched NRRW women in the two studies, women in the new study tend to have been exposed more recently, when mean annual doses were lower (Table A6).

5.2 Overall comparison with earlier findings

In the original study (Draper et al, 1997a,b), the risk of childhood cancer in the offspring of female radiation workers was statistically significantly greater than that among the offspring of non-radiation workers. For all childhood cancers taken together, the relative risk in the offspring of female radiation workers compared to those of control mothers was 5.0 (95% CI: 1.42 to 26.94), based on 15 cases and 3 controls. The main motivation for conducting this new study was to determine whether these elevated risks would be found in later data. The new data do not support the association seen previously. In the new data there were 4 cases and 7 controls among the offspring of female radiation workers. Indeed, tests for heterogeneity revealed a significant difference (χ^2 on 1 d.f. =4.75, P=0.03) in the relative risks for childhood cancer overall between the new data and the original data, suggesting that we should interpret results taken from the pooled dataset with caution. The influence of the earlier data means that the relative risk for the pooled data of 1.9 is still above one, but the elevation is not significant.

It is thus doubtful that there is any elevated risk of childhood cancer in the offspring of female radiation workers generally. If such a risk exists it now seems likely that it is of about the same magnitude as that in the offspring of male workers (Draper et al, 1997a,b; Sorahan et al, 2003). In that group the relative risk of LNHL was significantly raised at 1.77 (95% CI: 1.05 to 3.03), while the relative risk for other cancers was not significantly different from one. For the male workers, studies of employment timing suggested that any excess in LNHL was consistent with an explanation involving population mixing. A similar analysis has been undertaken for women despite the small number of cases and this is discussed below.

A number of other analyses were carried out. For example, childhood cancer risks were assessed among the offspring of mothers monitored for internal exposure as compared with other workers and of industrial workers versus non-industrial workers. In the original data only one woman (the mother of a control child) had been monitored for internal exposure. In the new data 4 women (the mothers of 3 cases and 1 control) had been monitored for internal exposure, so – as before - the numbers are too small to draw any reliable conclusions. As in the original study, there were no statistically significant differences in risk between the offspring of industrial and non-industrial workers, either in the new or in the pooled data.

We also discuss the results for women who worked during the period of pregnancy. The results for this group from the original study were not statistically significant and a further examination of this question was not a main reason for undertaking the current study. However, the pooled data give a raised relative risk which approaches statistical significance, though this is based on very small numbers. We feel that any such possible risk must be taken seriously, not least because of changes in the employment patterns of female radiation workers. A comparison of the original and new datasets suggests that there has been a change in women's employment patterns within the nuclear industry. It seems that in the earlier years, women tended to work for a shorter period of time, finishing work some time before the child in question was born and frequently not returning to work, whereas in more recent times women are in

employment, often as monitored workers, for most of the period prior to childbirth and frequently subsequently return to work. In the original study only a few of the NRRW women identified as case or control mothers (4 out of 18, 22%) were exposed while pregnant, whereas in the new data 4 out of 11 such linked women (36%) were exposed while pregnant. If indeed more women are continuing in radiation work while pregnant, it is important that accurate estimates of any possible childhood cancer risk incurred by their subsequent children are available. This issue is discussed further in section 5.4.

5.3 Effect of employment timing

Since there have been many more male than female radiation workers, the results from the original study for the offspring of male radiation workers were based on much larger numbers - and hence were more precise – than the corresponding findings for the offspring of female radiation workers. In the original study there was a statistically significant excess of LNHL in the offspring of male radiation workers (Draper et al, 1997a,b). However, a subsequent exploration of the way that this excess was distributed between the offspring of men who had left radiation work before conception of the child in question and those still employed on the date of conception showed that the excess was concentrated in the latter (Sorahan et al, 2003). This was consistent with the idea that any causative factor was one that operated among the population around a nuclear site, rather than being carried with a worker when he left (as might be expected of unrepaired radiation-induced damage to genetic material). The finding thus lent support to the idea that an infective mechanism, operating in the remote areas in which nuclear sites tend to be situated, might be largely responsible for elevated levels of childhood leukaemia. This explanation is reasonably persuasive, since the original observed excess of LNHL in the offspring of male radiation workers was of about the magnitude of other excesses attributed to population mixing (Kinlen, 1995, 1997).

Possible explanations of the raised risk among children of women radiation workers found in our earlier study are that it was due either to chance or to some other aetiological factor, for instance that it was related to exposure to infection. The possibility that the finding was simply due to chance is strengthened by the fact that the tumours observed in the offspring of women radiation workers are in different diagnostic categories. However, it is possible that some small effect of population mixing may be taking place. There is good evidence that childhood leukaemia is related to exposure to infection (McNally and Eden 2004) and some indirect evidence that this might also be true for other childhood cancers. The Seventh Report of the Committee on Medical Aspects of Radiation in the Environment (Paragraph 7.10, COMARE 2002) suggested "it is possible that infection related to population mixing might have a more general role than originally suggested [i.e. that it might apply to other diagnostic groups in addition to childhood leukaemia] but evidence for this suggestion is lacking". The series of studies by Kinlen referred to in the Introduction has shown that childhood leukaemia is increased in situations where there is a high level of population mixing, leading possibly to exposure of a susceptible population to a leukaemagenic virus or viruses, but these studies appear to offer no evidence that population mixing is relevant to other childhood cancers. However, analyses carried out for COMARE (2006) found that incidence rates for some other childhood cancers were related to levels of measures of socio-economic

status, which are likely to be related to a number of other possible aetiological factors including exposure to infections.

In this new study of the offspring of female radiation workers, no effect of employment timing is seen (Table 3). This may well be a consequence of the small number of cases. While the relative risks based on whether the mother had stopped employment at an NRRW-participating facility before the child's conception or was still employed at this time were not statistically significantly different from one, the associated confidence intervals were wide. We should therefore bear in mind the possibility that somewhat elevated levels of LNHL may be found in the offspring of female radiation workers for this reason. However, women leaving nuclear industry employment may be more likely than men to remain living in the vicinity of a nuclear installation; in this case the leukaemia risks for their offspring would not be related to patterns of employment.

5.4 *In utero* exposure

Case control differences for childhood cancer overall for children receiving an *in utero* dose were similar in the new and original datasets. However, while the pooled relative risk for these children is of borderline significance (p=0.07), the evidence is limited because of the small numbers of linked cases and controls.

It is important to compare our results with those of studies of the possible carcinogenic effects of medical diagnostic radiation during pregnancy (Stewart et al, 1956; MacMahon, 1962). It is now widely accepted that the associations observed in such studies reflected a causal relation and that very low exposures to x-rays resulted in an increased risk of both leukaemia and other childhood cancers. Various authors (Bithell and Stewart, 1975; Stewart and Kneale, 1970; Bithell and Stiller, 1988; Muirhead and Kneale, 1989) give estimates of the risk in relation to estimated foetal doses for the Oxford Survey of Childhood Cancers (OSCC) though the dosimetry for that study is very imprecise. The most recent review of these data is that by Wakeford and Little (2003). These authors conclude that the excess relative risk of childhood cancer resulting from *in utero* exposure may be estimated from the OSCC data as 50 per Gy, i.e. 0.05 per mGy [*]. They remark that there is appreciable uncertainty in this estimate and that there is reason to believe that it could be an overestimate.

In general the doses to the foetus as a result of occupational exposures would have been lower than those in the OSCC, though there is likely to be some overlap.

There are also important differences between the studies: for instance, the doses in the obstetric radiation studies differ from those in the present study in that the former were delivered by one or a few instantaneous exposures, whereas doses in the present study were probably usually delivered over a period of weeks or months. The obstetric exposures occurred predominantly in the third trimester of pregnancy, while most of the occupational exposures are likely to have been earlier. The relative risk of 7.0 that we have found for *in utero* exposures is almost statistically significant. In fact, for a one-

[*] For x-rays, 1 mGy is taken to be equivalent to 1 mSv.

tailed test, which is arguably more appropriate, $p<0.05$. However, if the risk were really so high, then this should have been apparent from the OSCC, i.e. the findings of the obstetric radiology studies appear to be quantitatively inconsistent with our observations. There are various possible explanations for this apparent anomaly: first, the finding may simply be due to chance or confounding; second, the risks may, as has been suggested (Bithell and Stewart, 1975), be greater for exposures in early pregnancy than for the mainly third trimester exposures in the OSCC data; third, as suggested by the width of the confidence interval, our estimate of 7.0 is consistent with a much lower level of risk. Another reason for a cautious interpretation of our results is that the *in utero* doses from maternal occupational exposures reported here are, on average, less than the total dose from natural radiation during the pregnancy, which – based on the assessment by Simmonds et al (1995, Appendix E, Tables E1(g) and E2(h)) – can be estimated to be around 0.8 mSv. In view of the small numbers involved we cannot conclude that our findings indicate a causal relation to radiation; the small increase in childhood cancer risk may well be due to chance.

5.5 Other epidemiological studies of childhood cancer and maternal radiation exposure

Published studies considering parental preconception irradiation predating our original study were reviewed at the time of that publication (Draper et al, 1997a, 1997b). The majority of the studies discussed covered paternal exposure and those few studies that did look at the effects of maternal preconception irradiation found no significant excesses of childhood malignancy. Since then, the Nuclear Industry Family Study (NIFS), an interview study, has reported on several aspects of the health of nuclear workers and their families including cancer in the children of employees (Roman et al, 1999) The design of their study differed substantially from that of our current and original studies : employees had to be working for one of three major nuclear industry employers at the time of data collection (1993 to 1996) and former employees were included in the study only if they were on the pension roll. Although NIFS recorded details of childhood tumours in the offspring of female employees, only 2 tumours in the offspring of exposed women workers were identified and the NIFS found a relative risk of 1.5 (not statistically significantly raised).

Some exposed occupational groups normally including a higher proportion of women are not covered by the NRRW and it is unfortunate that our study was not able to include these women. One such group is medical radiographers; however a study of this group (Roman et al, 1996) found no excess cancer in the offspring of the women workers who formed around 90% of the workers participating in the study.

An American study of areas around three nuclear facilities in the United States (Sever et al, 1997) considered the association between parental exposure to ionising radiation and childhood cancer. Although intended primarily to replicate the approaches used by Gardner et al (1990a, b) and McLaughlin et al (1993), the study also examined the risk of maternal preconception exposure for various cancer diagnostic subgroups. A non-significantly raised relative risk of 2.57 (95% CI: 0.67-9.83, based on 4 cases and 7 controls) was found for central nervous system tumours in offspring of women employed

prior to conception at one of the 3 sites. No significantly raised risks for leukaemia or LNHL were reported in the American study. Only one of the three facilities reported non-zero maternal doses during pregnancy. Based on six exposed mothers, there was a non-significantly increased risk for all cancers combined with an indication that the case mothers had received higher doses.

Kallen et al (1998) considered childhood cancer and other reproductive outcomes in the offspring of Swedish women treated with radiotherapy for skin haemangioma in infancy (before the age of 18 months). The study found no excess of childhood malignancies and no dose response relationship in the offspring of these women. There have been a number of other studies of possible untoward effects, including malignant disease, of the offspring of patients treated with radiation, often combined with chemotherapy. However, the report of a recent international workshop (Wyrobek et al, 2007) concluded that "no human germ-cell mutagen has been confirmed to date".

6 CONCLUSIONS

Considerable attention has been given to the possibility that the risk of childhood cancer may be affected by parental radiation exposure to carcinogens in the workplace. This report has examined whether there is an increased risk of childhood cancer in the offspring of mothers occupationally exposed to radiation before the conception of their children, by using more data than were available previously. This study benefited from linking - in an unbiased manner – the large National Registry of Childhood Tumours and a database of matched controls to the large National Registry for Radiation Workers. Nevertheless, the strength of the conclusions is limited by the small numbers of radiation workers found among the mothers of childhood cancer cases and controls, both in the original and in the new dataset. The following conclusions can be drawn:

1. Within the new dataset no statistically significant association was observed between maternal preconception exposure and risk in subsequent children of leukaemia and non-Hodgkin lymphoma, other cancers, or all cancers combined.

2. Neither the new nor the pooled data support the suggestion from the earlier study of a raised risk of childhood cancer in the offspring of female radiation workers.

3. In our earlier study, which was concerned primarily with male radiation workers, we found that the risk of LNHL was concentrated in the offspring of male workers who were employed on the date of conception. This risk might therefore be attributable to some aspect of employment pattern rather than genetic damage. In the present study of female workers we do not find a significantly raised risk for any employment period or diagnostic grouping. However, the small numbers of cases means that it is difficult to draw conclusions regarding the effect of employment patterns.

4. Considering *in utero* exposure, a weak association was found between maternal radiation work during pregnancy and childhood cancer in offspring in the pooled data. However, the evidence is limited because of the small numbers of linked cases and controls involved.

7 ACKNOWLEDGEMENTS

We acknowledge the help of Charles Stiller and other CCRG staff in maintaining the NRCT. We are also grateful to the consultants and general practitioners who routinely provide the information on which the NRCT is based, and to ONS, ISD, GRO(S), the regional cancer registries and the Children's Cancer and Leukaemia Group. We also wish to express our thanks to the workforces and managements of the organisations participating in the NRRW and to their Dose Record Keeping Services for their cooperation with this study.

The work of the CCRG is supported by the Department of Health for England and Wales and the Scottish Ministers.

Specific support for this study was received from the Department of Health's Radiation Protection Research Programme.

8 REFERENCES

Bithell JF and Stiller C (1988). A new calculation of the carcinogenic risk of obstetric X-raying. *Statistics in Medicine*, **7**: 857–864.

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

Britcher AR, Bartlett DT and Burgess PH (1991). The measurement of occupational exposure to ionising radiation: principles and practice. *J Radiol Prot,* **11**: 185-190.

Bunch KJ, Muirhead CR, Draper GJ, Hunter N, Kendall GM, O'Hagan JA, Phillipson MA, Vincent TJ and Zhang W (2009). Cancer in the offspring of female radiation workers: a record linkage study. *Br J Cancer*, **100**: 213-8.

Carpenter L, Higgins C, Douglas A, Fraser P, Beral V and Smith, P (1994). Combined analysis of mortality in three United Kingdom nuclear industry workforces. *Radiat Res,* **138:** 224-238.

Committee on the 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 the 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 the Medical Aspects of Radiation in the Environment (COMARE) (2006). Eleventh Report. *The distribution of childhood leukaemia and other childhood cancers in Great Britain 1969-1993.* NRPB, Chilton.

Duncan KP and Howell RW (1970). Health workers in the United Kingdom Atomic Energy Authority. *Health Phys*, **19**: 285-291.

Draper GJ, Little MP, Sorahan T, Kinlen LJ, Bunch KJ, Conquest AJ, Kendall GM, Kneale GW, Lancashire RJ, Muirhead CR, O'Connor CM and Vincent TJ (1997a). Cancer in the offspring of radiation workers: a record linkage study. *Br Med J,* **315**: 1181-1188.

Draper GJ, Little MP, Sorahan T, Kinlen LJ, Bunch KJ, Conquest AJ, Kendall GM, Kneale GW, Lancashire RJ, Muirhead CR, O'Connor CM, Vincent TJ, Thomas JM, Goodill AA, Vokes J and Haylock RGE (1997b). *Cancer in the offspring of radiation workers – a record linkage study.* Chilton, NRPB-R298.

Gardner MJ, Hall AJ, Snee MP, Downes S, Powell CA and Terrell JD (1990a). Methods and basic data of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J***, 300**: 429-434.

Gardner MJ, Snee MP, Hall AJ, Powell CA, Downes S and Terrell JD (1990b). Results of case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J*, **300**: 423-429.

Gardner MJ (1992). Paternal occupations of children with leukaemia. *Br Med J,* **305**: 715.

Howe GR (1985). Use of computerized record linkage in follow-up studies of cancer epidemiology in Canada. *J Natl Cancer Inst Monogr*, **67**: 117-121.

Kallen B, Karlsson P, Lundell M, Wallgren A and Holm L-E (1998). Outcome of reproduction in women irradiated for skin hemangioma in infancy. *Radiat Res*, **149**: 202-208.

Kendall GM, Muirhead CR, MacGibbon BH, O'Hagan JA, Conquest AJ, Goodill AA, Butland BK, Fell TP, Jackson DA, Webb MA, Haylock RGE, Thomas JM and Silk TJ (1992). Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *Br Med J*, **304**: 220-5.

Kinlen LJ (1988). Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet,* **ii**(8624): 1323-7.

Kinlen LJ, Clarke K and Balkwill A (1993). Paternal preconceptional radiation exposure in the nuclear industry and leukaemia and non-Hodgkin' lymphoma in young people in Scotland. *Br Med J,* **306**: 1153-1158.

Kinlen LJ (1995). Epidemiological evidence for an infective basis in childhood leukaemia. *Br J Cancer*, **71**: 1-5.

Kinlen LJ (1997). High-contact paternal occupations, infection and childhood leukaemia: five studies of unusual population-mixing of adults. *Br J Cancer,* **76**: 1539-45.

LogXact (2005). *LogXact. A statistical package for regression procedures featuring exact methods (Version 7.0).* Cytel Software Corp: Cambridge, Massachusetts.

MacMahon B (1962). Prenatal x-ray exposure and childhood cancer. *J Natl Cancer Inst*, **28**: 1173-1191.

Mehta CR and Patel NR (1995). Exact logistic regression: theory and examples. *Statistics in Medicine,* **14:** 2143-2160.

McLaughlin JR, King WD, Anderson TW, Clarke EA and Ashmore JP (1993). Paternal radiation exposure and leukaemia in offspring: the Ontario case-control study. *Br Med J*, **307**: 959-966

McNally RJQ and Eden TOB (2004). An infectious aetiology for childhood acute leukaemia: a review of the evidence. *Br J Haematol*, **127**, 243-263.

Muirhead CR, Goodill AA, Haylock RGE, Vokes J, Little MP, Jackson DA, O'Hagan JA, Thomas JM, Kendall GM, Silk TJ, Bingham D and Berridge GLC (1999a). Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. *J Radiol Prot,* **19**: 3-26.

Muirhead CR, Goodill AA, Haylock RGE, Vokes J, Little MP, Jackson DA, O'Hagan JA, Thomas JM, Kendall GM, Silk TJ, Bingham D and Berridge GLC (1999b). *Second analysis of the National Registry for Radiation Workers: Occupational exposure to ionising radiation and mortality.* Chilton, NRPB-R307.

Muirhead CR, O'Hagan JA, Haylock RGE, Phillipson MA, Willcock T, Berridge GLC and Zhang W (2009). Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*, **100**: 206-12.

Muirhead CR and Kneale GW (1989). Prenatal irradiation and childhood cancer. *J Radiol Prot,* **9**: 209-212.

Newcombe HB (1988). *Handbook of Record Linkage: Methods for Health and Statistical studies, Administration and Business.* Oxford Medical Publications. Oxford University Press, Oxford.

Riddell AE, Battersby WP, Peace MS and Strong R (2000). The assessment of organ doses from plutonium for an epidemiological study of the Sellafield workforce. *J Radiol Prot,* **20**: 275-286.

Roman E, Doyle P, Ansell P, Bull D, and Beral V (1996*).* Health of children born to medical radiographers. *Occup Environ Med*, **53**: 73-79.

Roman E, Doyle P, Maconochie N, Davies G, Smith PG and Beral V (1999). Cancer in children of nuclear industry employees: report on children aged under 25 years from nuclear industry family study. *Br Med J,* **318**: 1443-50.

Sever LE, Gilbert ES, Tucker K, Greaves JA and Buchanan J (1997). *Epidemiological evaluation of childhood leukaemia and paternal exposure to ionising radiation.* Final report dated 9 October 1997. Centers for Disease Control, Cooperative Agreement U50/CCU012545-01.

Simmonds JR, Robinson CA, Phipps AW, Muirhead CR and Fry FA (1995). Risks of leukaemia and other cancers in Seascale from all sources of ionising radiation exposure. Chilton, NRPB-R276.

Sorahan T, Haylock RGE, Muirhead CR, Bunch KJ, Kinlen LJ, Little MP, Draper GJ, Kendall GM, Lancashire RJ and English MA (2003). Cancer in the offspring of radiation workers: an investigation of employment timing and a reanalysis using updated dose information. *Br J Cancer*, **89:** 1215-1220.

Stewart A, Webb J, Giles D and Hewitt D (1956). Malignant disease in childhood and diagnostic irradiation *in utero*. *Lance*t, **ii**: 447.

Stewart A and Kneale GW (1970). Radiation dose effects in relation to obstetric x-rays and childhood cancer. *Lancet*, **i**(7658): 1185-1188.

Stiller C (2007). *Childhood cancer in Britain: incidence, survival, and mortality.* Oxford: Oxford University Press.

Wakeford R and Little MP (2003). Risk coefficients for childhood cancer after intrauterine irradiation: a review. *Int J Radiat Biol*, **75**: 293-309.

Wyrobek AJ, Mulvihill JJ, Wassom JS, et al. (2007). Assessing Human Germ-Cell Mutagenesis in the Post-Genome Era: A Celebration of the Legacy of William Lawson (Bill) Russell. *Environ Mol Mutagen*, **48**: 71-95.

9 ABBREVIATIONS AND ACRONYMS

AWE	Atomic Weapons Establishment
BEIR	(US Committee on the) Biological Effects of Ionizing Radiation
BNFL	British Nuclear Fuels plc
CCLG	Children's Cancer and Leukaemia Group
CI	Confidence Interval
CMLE	Conditional Maximum Likelihood Estimate
CNS	Central Nervous System
ERR	Excess Relative Risk
GRO(S)	General Register Office for Scotland
HPA	Health Protection Agency
HPA-RPD	HPA's Radiation Protection Division
ICRP	International Commission on Radiological Protection
ISD	Information and Statistics Division of the Scottish Health Service
LNHL	Leukaemia and non-Hodgkin lymphoma
MoD	Ministry of Defence
MRC	Medical Research Council
MUE	Median Unbiased Estimate
NHL	Non-Hodgkin Lymphoma
NICEA	Nuclear Industry Combined Epidemiological Analysis
NRCT	National Registry of Childhood Tumours
NRPB	National Radiological Protection Board (now HPA-RPD)
NRRW	National Registry for Radiation Workers
ONS	Office for National Statistics

PPI	Parental Preconception Irradiation
RR	Relative Risk
STFC	Science and Technology Facilities Council
UKAEA	United Kingdom Atomic Energy Authority
UKCCSG	United Kingdom Children's Cancer Study Group

APPENDIX A Number of Cases in Registers

A1 DETAILS OF NRCT REGISTERS

Table A1: Details of birth record requests

England, Wales and Scotland: number of eligible cases	18,179	(100%)
Traced	16,964	(93.3%)
Not available: known to be adopted or born abroad	402	(2.2%)
No trace at ONS/GRO(S) (including those found to be born abroad or adopted)	813	(4.5%)

A2 TABLES RELATING TO NRRW

Table A2: Distribution of workers by first employer

Employer / site	No. of women
BNFL	**3320**
Capenhurst	84
Chapelcross	121
Sellafield	2482
Springfields	547
Other	86
GE Healthcare	**1553**
MOD, including AWE	**7331**
AWE	1704
MOD	5627
Nuclear Power Supply companies	**409**
England/Wales sites	313
Scottish sites	96
Rolls Royce Submarines	**302**
STFC/MRC/HPA-RPD	**332**
UKAEA	**2580**
Dounreay	565
Harwell	1570
Winfrith	257
Other	188
Other	**13**
TOTAL	**15840**

Table A3: Number of employments per individual

Employments	Number of women	Percentage
1	14851	94%
2	892	6%
3	84	1%
4	11	0%
5	2	0%
TOTAL	**15840**	

Table A4: Distribution of workers by year of birth

Birth years	Number of women	Percentage
Pre - 1915	315	2%
1915 - 1919	199	1%
1920 - 1924	443	3%
1925 - 1929	544	3%
1930 - 1934	779	5%
1935 - 1939	1018	6%
1940 - 1944	1129	7%
1945 - 1949	1069	7%
1950 - 1954	1248	8%
1955 - 1959	2138	13%
1960 - 1964	2394	15%
1965 - 1969	2342	15%
1970 - 1974	1718	11%
1975 - 1979	461	3%
1980 - 1984	43	0%
TOTAL	**15840**	

Table A5: Distribution by worker's lifetime dose

Dose range (mSv)	Number of women	Collective dose (person mSv)	Mean lifetime dose (mSv)
<10.0	12826	29714.3	
10.0-49.9	2636	50529.4	
50.0-99.9	274	18191.2	
100.0-	104	17886.0	
Total	**15840**	**116320.9**	**7.3**

Table A6: Distribution of workers mean annual dose by calendar period

Period	Women Years	Collective dose (person Sv)	Mean annual dose (mSv)
1945-1949	284	0.8	2.8
1950-1954	1373	4.6	3.4
1955-1959	2738	8.8	3.2
1960-1964	3725	10.0	2.7
1965-1969	3365	7.9	2.3
1970-1974	3890	9.9	2.5
1975-1979	8908	18.9	2.1
1980-1984	13349	19.3	1.4
1985-1989	16438	16.4	1.0
1990-1994	18467	12.0	0.7
1995-1999	17314	7.8	0.4
Total	**89851**	**116.3**	**1.3**

APPENDIX B Aspects of Statistical Methods

B1 EXACT METHODS OF INFERENCE FOR LOGISTIC REGRESSION

This appendix summarises the methodology underlying the analysis of case-control data using exact methods of statistical inference. Cox (1970) originally outlined the general theory for exact methods for logistic regression, which is based on generating the exact permutational distributions of the sufficient statistics for the regression parameters of interest, conditioning on the observed values of the sufficient statistics for all the remaining parameters. This approach was not considered computationally feasible until the development of fast algorithms for deriving these distributions (Mehta and Patel, 1995).

Assume that the data consist of *k* matched case-control sets. Suppose that the *i* th set contains one case with the disease under investigation and m_i matched controls who were at risk of developing the disease at around the same time but did not do so. Let the response $Y_{ij} = (Y_{i0}, ..., Y_{i m_i})$ be the vector of case control indicators for the *i* th set, where $Y_{ij} = 1$ if the *j*th subject is a case and $Y_{ij} = 0$ for a control $(0 \le j \le m_i, 1 \le i \le k)$ and also let x_{ij} be a vector of covariates (explanatory variables) for subject *j* in the *i*th set. The logistic regression model for exploring the relationship between the covariates and response is

$$\log(\theta_{ij} / (1 - \theta_{ij})) = \gamma_i + \beta\ x_{ij},$$

where θ_{ij} = Pr $(Y_{ij} = 1 | x_{ij})$ (ie. the probability that the *j*th subject in set i is a case) and γ_i and $\beta = (\beta_0, \beta_1, ..., \beta_p)$ are unknown parameters common across all *k* sets. We are interested in estimating *β* only. The set effects γ_i are eliminated from the likelihood function by conditioning on the number of cases per matched set. As discussed by Mehta and Patel (1995), exact inference is based on the sufficient statistic for *β*, that is, $\mathbf{t} = \sum_{i=1}^{k} \sum_{j=0}^{m_i} Y_{ij}\ x_{ij}$ and the conditional likelihood is

$$L = \Pr(T_0 = t_0, T_1 = t_1, T_2 = t_2, ..., T_p = t_p) = \frac{c(\mathbf{t})\ \exp(\beta \mathbf{t})}{\sum_{\mathbf{u}} c(\mathbf{u})\ \exp(\beta \mathbf{u})} \qquad (1)$$

where $c(t) = |S_k(t)|$, $S_k(t) = \{y_{ij}, j = 0, ..., m_i, i = 1, ..., k : \sum_{i=1}^{k} \sum_{j=0}^{m_i} Y_{ij}\ x_{ij} = \mathbf{t}, \sum_{j=0}^{m_i} Y_{ij} = 1\}$,

with |*S*| denoting the number of distinct elements in *S* and the sum is over all *u* for which $c(\mathbf{u}) \ge 1$.

Assume that we wish to estimate the single parameter β_p. Let $f(t_p \mid \beta_p)$ denote the conditional probability $\Pr(T_p = t_p \mid T_0 = t_0, T_1 = t_1, \ldots, T_{p-1} = t_{p-1})$. Then

$$L = f(t_p \mid \beta_p) = \frac{c(t_0, t_1, t_2 \ldots, t_p)\ \exp(\beta_p t_p)}{\sum_{u=t,\min}^{t,\max} c(t_0, t_1, t_2 \ldots, t_{p-1}, u)\ \exp(\beta_p u)} \qquad (2)$$

with the summation over all values *u* for which $c(t_0, t_1, t_2 \ldots, t_{p-1}, u) \geq 1$. The exact logistic regression estimate β_p is the value that maximises this conditional likelihood.

The exact P-value for a significance test can be obtained by summing the probability of the observed outcomes over some specified critical region, *R*, which depends on the type of exact test selected; for example, whether this is the exact conditional score test or the exact conditional likelihood ratio test.

$$P = \sum_{v \in R} f(v \mid \beta_p = 0)$$

To obtain a 95% confidence interval (β_{lower}, β_{upper}) for β_p, let t_{min} and t_{max} be the smallest and largest possible values of t_p in the distribution (Eq.2). The lower confidence bound, β_{lower}, is such that

$$F_1(t_p \mid \beta_{lower}) = 0.025 \quad if\ t_{\min} < t_p \leq t_{\max}$$
$$\beta_{lower} = -\infty \qquad if\ t_p = t_{\min}$$

Similarly the upper confidence bound, β_{upper}, is such that

$$F_1(t_p \mid \beta_{upper}) = 0.025 \quad if\ t_{\min} \leq t_p < t_{\max}$$
$$\beta_{upper} = \infty \qquad if\ t_p = t_{\max}$$

A point estimate for β_p is obtained in one of two ways. Exact inference first attempts to obtain the conditional maximum likelihood estimate (CMLE), β_{CMLE}, by maximising the conditional probability $f(t_p \mid \beta_p)$ with respect to β_p. If, however, t_p is equal to either t_{min} or t_{max}, then β_{CMLE} is undefined, since the conditional likelihood cannot be maximised. In this instance, an alternative estimate for β is the median unbiased estimate (MUE),

$$\beta_{MUE} = (\beta_{upper} + \beta_{lower}) / 2$$

where we evaluate β_{lower} and β_{upper} at a confidence level α = 0.05. If $\beta_{lower} = -\infty$, we define $\beta_{MUE} = \beta_{upper}$, while if $\beta_{upper} = \infty$, we define $\beta_{MUE} = \beta_{lower}$. Thus unlike the conditional maximum likelihood estimate, the median unbiased estimate is always defined, even at the extreme points of the sample space.

B2 CALCULATING P-VALUES USING DEVIANCE STATISTICS

A deviance goodness of fit test provides an assessment of the adequacy of a fitted model (McCullagh and Nelder, 1989). Under the null hypothesis that the reduced model under consideration fits as well as a fuller model, the difference in the deviance between the two models has asymptotically a chi-squared distribution with degrees of freedom equal to the difference in the number of parameters in the two models being compared. However, this approximation may not be adequate if the data are sparse.

The exact test due to Mehta and Patel (1995) uses a different approach to calculating P-values using deviance statistics. This involves identifying the region of the sample space for which the deviance difference is at least as great as the observed value. The exact P-value is then calculated as the probability under the null hypothesis (ie. that the reduced model fits as well as the full model) of obtaining a result that falls within this sample space, conditional on the sufficient statistics for the model parameters (as described in Appendix B1). This P-value can be calculated using LogXact (2005).

References

Cox DR (1970). *Analysis of Binary Data*, Chapman and Hall, London.

LogXact (2005). *LogXact. A statistical package for regression procedures featuring exact methods (Version 7.0).* Cytel Software Corp: Cambridge, Massachusetts.

Mehta CR and Patel NR (1995). Exact logistic regression: theory and examples. *Statistics in Medicine,* **14:** 2143-2160.

McCullagh P and Nelder JA (1989). *Generalized Linear Models, 2nd edition*, Chapman and Hall, London.