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EPIDEMIOLOGIC EVALUATION OF CHILDHOOD LEUKEMIA AND PATERNAL EXPOSURE TO IONIZING RADIATION

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BACKGROUND

This project examined cases of three major categories of childhood cancers in the populations around three United States Department of Energy (DOE) facilities to examine the hypothesis of an association between childhood cancer risk and paternal preconception occupational radiation exposure. This hypothesis was based on the finding of such an association in the population around the Sellafield nuclear facility in England (Gardner et al. 1990a).

In an attempt to identify the cause of a cluster of childhood cancers in the vicinity of the Sellafield nuclear plant in West Cumbria, Gardner et al. (1990a, 1990b) conducted a case-control study of cases of leukemia and non-Hodgkin's lymphoma. Examining a wide variety of risk factors, the authors demonstrated that relative risks for leukemia and non-Hodgkin's lymphoma were higher in children born near Sellafield and in children of fathers employed at the facility, particularly fathers with high radiation dose recordings before conception.

Gardner et al. (1990a, 1990b) included all known cases of leukemia and non-Hodgkin's lymphoma among residents of the West Cumbria Health Authority who were diagnosed between the years of 1950 and 1985, were born in the area, and were under the age of 25 years at the time of diagnosis. Cases were ascertained using a variety of sources. The investigators attempted to select eight "area" controls and eight "local" controls for each case from the birth register where the case's birth was recorded. Controls selected were births of the same sex as the case whose entries in the birth register were closest in time to those of the case and whose mothers resided in West Cumbria at the time of the birth (area controls), or whose mothers resided in the same civil parish as the case (local controls). Some controls fell into both groups.

Potential controls were excluded who had died or were not resident in West Cumbria at the date of cancer diagnosis of the case to whom they were matched.

Data on possible risk factors were obtained for cases and controls from a variety of sources, including obstetric records, birth certificates, maternal and paternal questionnaires, and Sellafield employment records. Information on father's occupation, as recorded on the birth certificates, was obtained for most children. For linkage with Sellafield records, information on the father's date of birth was obtained for 91% of cases and controls.

Among 46 children with leukemia, 4 of their fathers had cumulative exposure levels above 100 mSv, compared to 5 of 288 for controls, a relative risk of 6.2 (95% confidence limits 1.5, 26). In addition to the risk associated with cumulative doses above 100 mSv, there appeared to be an increased risk with doses above 10 mSv during the 6 months immediately before conception. Differences between case and control fathers in terms of dose were highly statistically significant. Even if analyses are restricted to offspring of those fathers who had been recorded as ever having had a "positive" external radiation dose, there is a marked difference in exposure histories between cases and controls.

Potential public health implications of a causal basis for the association reported by Gardner et al. (1990a) are great, as is indicated by the extent of public, media, and scientific response to their publication (Aldhous 1990; Anderson 1990; Milne 1990; Roberts 1990; Sever 1991). The initial scientific response was directed at attempting to understand potential mechanisms for such an effect, which does not fit well with general concepts of radiation health risks or leukemia etiology (Fogle 1990; Roberts 1990). Responses by workers, the public, and

the media were concerns about risks to worker's children associated with occupational exposure to ionizing radiation at levels generally considered safe.

In an editorial that accompanied the Gardner et al. papers, Beral (1990) indicated that implications of this study regarding potential risks of adverse health effects among workers with low-level exposures below current limits are sufficiently important to warrant further investigation. In Science on April 6, 1990, it is stated that "What's urgently needed, everyone agrees, is to replicate Gardner's study with U.S. radiation workers" (Roberts 1990). According to David Hoel (Roberts 1990) such a study is a top priority "to see if we need to rethink exposure limits for workers and to get at the biology of it." Daniel Hoffman of the Centers for Disease Control is quoted as saying "the main thing now is to get replication with the large cohort of DOE and (U.S.) nuclear plant workers" (Anderson 1990).

Addressing the questions raised by the Gardner et al. (1990a) study, in August 1992, a report was issued by the Atomic Energy Control Board of Canada with results of a case-control study of fathers' occupational ionizing radiation exposure and childhood leukemia in Ontario, Canada (McLaughlin et al. 1993). This study was conducted using leukemia cases in the vicinities of five nuclear facilities in Ontario.

The study employed a case-control design, with cases ages 0-14 at diagnosis between 1950 and 1988 and born to women who resided in the vicinity of an operating nuclear facility. A total of 112 cases was included in the study.

Birth certificate controls were matched to cases by date of birth and mother's residence at birth. Controls were identified by hand search through certificates before and after the case's birth to find a child born within 3 months of the case. Potential controls were linked to

mortality files to determine if potential controls were still alive at the age when the case was diagnosed. To be a control, the child had to survive to the age at which the case was diagnosed. Eight controls were selected for each case. The control group included 890 controls matched in this manner.

Fathers of the subjects were linked to occupational radiation records of the Canadian National Dose Registry (NDR). Missing names, initials, and birth date led to problems with linkage. Computer exposure histories were obtained from NDR records. Information on whole body dose and internal dose was obtained for lifetime and annual doses.

The findings of McLaughlin et al. (1993) do not support the hypothesis that childhood leukemia is associated with paternal occupational ionizing radiation exposure. The results are inconsistent with a relative risk of the order of magnitude identified by Gardner et al. (1990a). The Ontario study showed no association between childhood leukemia and occupational exposures to ionizing radiation of fathers before conception. Analyses looked at whole body dose, tritium dose, and radon exposures during three preconception periods; lifetime, six months, and three months prior to conception.

Urquhart et al. (1991) conducted a case-control study of leukemia and non-Hodgkin's lymphoma in the area around the Dounreay nuclear installation in Caithness, Scotland. 14 cases of leukemia and non-Hodgkin's lymphoma, diagnosed before age 15, were compared with 55 controls matched by sex, date of birth and mothers area of residence within Caithness at the time of birth. Paternal occupation and employment at Dounreay were determined from birth certificates and employment records. There was no evidence of increased risk associated with employment in the nuclear industry at the time of conception, at the time of birth, or at

diagnosis. Urquhart et al. (1991) observed no increased risk of leukemia and non-Hodgkin's lymphoma if the father's lifetime radiation dose at conception was 100+ mSv relative to < 100 mSv or if the paternal radiation dose in the 6 months prior to conception was 10+ mSv relative to < 10 mSv. There were no case vs. control differences in lifetime radiation dose prior to conception. This study was based on a small number of cases.

The study by Urquhart et al. (1991) was followed by a much larger case-control study of leukemia and non-Hodgkin's lymphoma in persons under 25, born in or after 1958 and diagnosed between 1958 and 1990, in all of Scotland (Kinlen, Clarke and Balkwill 1993). This dataset included all of the cases in the Caithness dataset. Fathers of these cases and fathers of a group of controls, selected randomly from the births of the same sex in the same year in the same county, were matched against records in the nuclear industry. There was no significant excess risk associated with paternal preconceptional radiation dose in terms of lifetime dose, dose 3 months prior to conception, or dose 6 months prior to conception.

The last study we describe is that conducted in West Berkshire and North Hampshire by Roman et al. (1993). Using a case-control design, Roman et al. (1993) studied leukemia and non-Hodgkin's lymphoma in children less than five at the time of their diagnosis. The study population included only children who were born and had their cancer diagnosed in the study area. Two groups of controls were selected, one group from the NHS birth registers and one from hospital delivery registers. Names of parents were checked against the employment and health physics records of the nuclear industry. Five of the 54 cases and 14 of the 324 controls had at least one parent who had been employed by the nuclear industry (RR 2.2, 95% CI 0.6-6.9). Three fathers of cases and two fathers of controls had been monitored for exposure to

external radiation before their child was conceived (RR 9.0, 95% CI 1.0-107.8) but no father had accumulated a recorded dose of >5 mSv before his child was conceived and no father had been monitored at any time in the four years before conception. The authors concluded that the association with monitoring for external radiation was unlikely to be due to the external radiation itself but that monitoring was indicative of potential for exposure to radionuclides that led to internal depositions

In summary, the studies discussed above fail to support the association between childhood cancer risk and paternal preconception radiation exposure demonstrated by Gardner et al. (1990a). Subsequent analyses of the Sellafield data showed that the risks associated with preconception radiation exposure were limited to offspring of the Sellafield workforce born in Seascale (HSE 1993; Little, Wakeford and Charles 1994). The risks in this group were highly statistically significantly different from the risks in the offspring of the Japanese atomic bomb survivors, the Canadian study of McLaughlin et al. (1993), the Scottish studies (Urquhart et al. 1991; Kinlen, Clarke and Balkwill 1993), and the offspring of the Sellafield workforce born outside Seascale (Little, Wakeford and Charles 1994). We will return to these points in the discussion of the results of the current study.

The publication of Gardner's initial study results was met with considerable skepticism on the part of many in the scientific community. Although there were no obvious major methodologic flaws in the conduct of the study, the findings were not consistent with much of the understanding of radiation health effects that had been developed over time. For some, the possibility that the associations between childhood leukemia risk and paternal radiation exposure that had been observed seemed far-fetched and unrealistic. For others, these findings confirmed

their beliefs that the health risks of low level radiation exposure were much greater than the scientific community had acknowledged. Finally, for some the data suggested a need to examine the issue of paternal preconception radiation exposure and childhood cancer risk more extensively. This latter interpretation was that held by the first author of this report and is consistent with published comments on the issue (Sever 1991) and with a decision by the Department of Energy and the Centers for Disease Control and Prevention to support research on this topic.

Since there have been other extensive reviews of the original Gardner et al. study and ensuing research (e.g., Doll, Evans and Darby 1994; Little et al. 1994; Wakeford 1995; Little, Charles and Wakeford 1995), in this report we present the methods and results of our research without an in-depth review of other work. In the discussion section we bring in a consideration of these other studies, as appropriate.

PROJECT OVERVIEW

In the seven years since the publication of Gardner's findings several additional studies have been conducted exploring the question using different approaches. The current case-control study was conducted using the populations around selected U.S. DOE nuclear facilities as the study population and linking cases of childhood cancers to worker records, attempting to replicate the approaches used by Gardner et al. (1990a, 1990b) and McLaughlin et al. (1993).

This study was carried out in three phases. The first phase was to conduct a pilot study at the Hanford Site in southeastern Washington State to test all aspects of a case-control study and to examine a number of issues related to the feasibility of the proposed design. The second

phase was to determine the feasibility of expanding the study to include other sites. The third phase was to conduct a case-control study at the additional sites found to be feasible in the second phase. This report discusses the design and conduct of the multi-site study. The methods used to conduct the study were comparable across the selected three sites, with some variability as it related to available data sources.

RESEARCH METHODS

Study Population

The at-risk study population was defined as the population in counties surrounding three D.O.E. nuclear facilities: The Hanford site (Hanford); Idaho National Engineering Laboratory (INEL); and K-25, Y-12, and X-10 at Oak Ridge, Tennessee (Oak Ridge). During the feasibility study phase we evaluated three sites in addition to Hanford: INEL, Oak Ridge, and the Savannah River Site in South Carolina. During this phase we determined that we could not get necessary medical records from one of the major hospitals that served the population around the Savannah River Site because access was denied. Therefore, the Savannah River Site was not included in the study.

The study counties selected for each of the three DOE nuclear facilities are as follow: Hanford -- Benton and Franklin; INEL -- Bannock, Bingham, Bonneville, Butte, Jefferson, and Madison; Oak Ridge -- Anderson, Knox, and Roane. These counties were selected on the basis of the fact that most of the workers at the sites reside there. Since our research hypotheses were related to employment at a nuclear site and subsequent exposure to ionizing radiation we wanted to identify the broad area where site workers live.

Case Definition

Cases were defined on the basis of diagnosis, year of diagnosis, age at diagnosis, and county of residence. The diagnoses included in the study included all types of leukemia, non-Hodgkin's lymphoma, and central nervous system tumors. Because of the small sample size, these aggregated categories were used in the analyses. Leukemia and non-Hodgkin's lymphoma were studied to replicate the types of cases studied earlier by Gardner et al. (1990a, 1990b) and McLaughlin et al. (1992). Central nervous system tumors were added to the diagnoses included in the study because of earlier associations between these tumors and paternal EMF exposure in some studies (Gold and Sever 1994) and because their cause(s) are unknown. Cases were eligible for inclusion in the study if they were diagnosed prior to age 15 during the years 1957-1991.

To be eligible for inclusion in the study a case had to have been born to residents of one of the study counties and be resident in one of the counties when their cancer was diagnosed. Residence at time of diagnosis was determined by reviewing the hospital record at time of diagnosis or initial treatment. When hospital records were unavailable, residence information was abstracted from tumor registries, death certificates, and city and telephone directories. Parental residence at birth was determined from the birth certificate.

Case Ascertainment

Cases were ascertained from each of the populations using multiple sources because no population-based cancer registries included all of the years 1957-1991. Sources of case ascertainment included local primary care hospitals, regional referral hospitals, cancer registries,

and death certificates. Each of these sources was utilized to provide as complete an ascertainment as possible. Requests were submitted to the individual sources asking them to search diagnostic indices and death indices using appropriate International Classification of Disease (ICD) codes. For hospital records, the actual record was reviewed to obtain identifying and diagnostic information. For cancer registries, computerized information was reviewed similarly. Copies of death certificates were obtained for those cases identified through the death indices.

Once a potential case was identified, and it met the case definition on the basis of information available from the ascertainment source, birth records were searched to determined if it met the county of residence at birth criterion. These searches involved both electronic birth files and review of hard copies of birth certificates at public health agencies.

Control Selection - Unrestricted Controls

Following the ascertainment of cases, a series of potential "unrestricted" controls was selected for each case. We use the term "unrestricted" to contrast this first group of controls -- generally referred to simply as controls -- with the second control group described below which is "restricted" to controls whose fathers were employed at one of the sites prior to the subject's conception. For each case, four controls were identified from birth certificates. To determine that these children remained at risk in the study area at least as long as their corresponding case, we established that their parents remained in the study counties at least until the control child reached the age at which the case was diagnosed.

Controls consisted of children identified from birth certificates matched to cases based on year of birth, county of residence, sex, race, and maternal age. Controls were matched on these variables in order to have a group which is as similar to the cases as possible in terms of leukemia risk factors and potential for parental exposure to ionizing radiation. County of residence was used as a matching criterion so the cases and controls would be similar in terms of probability of parental employment at one of the sites.

For Hanford, birth certificate controls were selected from a computer file of Benton and Franklin County births provided by the Technical and Data Services Section (TDSS), Center for Health Statistics, Washington State Department of Health. We identified all births that matched each case on the basis of year of birth, race, sex, and maternal age. A file of potential controls was developed that included all births matching each case. For these potential controls, the file includes data on the matching criteria plus the baby's name, names of both parents, the name of the mother before marriage, and residence (number, street, and town).

If during the randomization control selection process the number of potential controls matched to a case was less than 25, then the matching criteria were relaxed to obtain the remaining needed potential controls. The first matching criterion to be relaxed was maternal age, in the following manner.

- A 3 year span (1 yr older and 1 yr younger than case mothers age)
- A 5 year span (2 yrs older and 2 yrs younger than case mothers age)

If after relaxing maternal age a case still lacked 25 matched potential controls, the selection process was relaxed on year of birth by one year. For example, if a case was born in 1958 the

years of 1957 or 1959 could be searched. For a few cases (Asian and Native American) race was ignored in the matching criteria.

From this pool, we selected 25 potential controls for each case. Depending on the size of the control pool we typically pulled every second or third subject and listed them. To determine if the control remained in the area until the age of the case, names of parents were searched through city directories and telephone directories. This was done by reviewing the directories for the year the potential control would reach the age of the matching case. If parent(s) were found to have remained in the area, the child was eligible to be a control. The first 4 children who met length of residence criteria were then selected as controls.

For cases from the six counties around INEL a pool of 25 potential controls for each case was selected from birth certificate files by the Idaho Center for Vital Statistics. Matching criteria were relaxed, when necessary, using the approached described above for Hanford. The names of the parents of these potential controls were then searched against city directories and telephone books to determine if the parents remained resident in the area up until the control child reached the age at which the case was diagnosed.

For the cases from around Oak Ridge controls were selected from birth records by Oak Ridge Associated Universities (ORAU) and the Tennessee Department of Health Division of Vital Statistics. The selection, matching, and relaxation criteria were similar to those used at Hanford.

For the control children to have the same chance of developing cancer as cases, they must have lived up to the age at which the case's disease was diagnosed. Once it was determined that the parents remained in the community, we determined the vital status of the

potential control by searching their names against state death records. This is similar to the approach used by McLaughlin et al. (1993).

Control Selection - Restricted Controls

For each case whose father worked at one of the study sites prior to conception, we identified an additional four matched controls whose fathers also worked there. We refer to this second control group as "restricted controls" since they were restricted to children whose fathers were employed at the study sites. For studying radiation exposure history, this control group allows for a comparison among cohort members, analogous to the within-cohort comparisons of mortality among nuclear workers (Gilbert 1983). A number of advantages are similar as well, including relative sociodemographic homogeneity among the DOE workers, documentation of occupational exposures for all parents, particularly for ionizing radiation, in contrast to parents employed outside of DOE facilities whose exposures are largely unknown. For addressing the most important of Gardner's (1990a) findings regarding preconception ionizing radiation exposure of fathers, the comparison among offspring of employees is ideal. At the same time, it is of interest to study all cases of the selected cancers and to make comparisons with a broader representation of children from the community.

Following the selection of the initial controls at each site the second group of four controls, the restricted controls, was selected for each case whose father was employed at the site prior to the subject's conception. After the selection of unrestricted controls, the subjects remaining in the initial pool who had not been eliminated due to residence in the index year were potential restricted controls. Typically, the pools had to be expanded, however, to find controls

whose fathers worked at the site. The names of the fathers of these potential controls were linked to the site worker rosters to determine those fathers who had been employed there prior to the conception of the child. For Oak Ridge the father could have been employed at any of the three facilities identified earlier. This process continued until a second group of controls was identified who were matched to the cases not only on the basis of the initial matching criteria, except for race, but also on the basis of their father being employed at the site prior to conception. This provided a control group similar to the cases with regard to the potential for paternal radiation exposure and the availability of dosimetric data. The same individual was never used as both an unrestricted and a restricted control. Follow-up for residence and vital status was identical to that discussed above for unrestricted controls.

Data Collection

For all cases, information on diagnosis and cause of death, as appropriate, was abstracted from hospital records, tumor registries, and death certificates. The quality of diagnostic data was limited in the early years included in the study. Typically, tumor registries did not cover the early years of the study. Death certificates did not always allow identification of a hospital where diagnostic information might be located. Hospital records, including individual medical records, were sometimes available for the early years of the study. Pathology reports were reviewed to obtain the most accurate histologic data possible. In addition to diagnostic information, demographic information was abstracted from ascertainment sources. This included race, sex, and age, along with address at diagnosis.

Copies of birth certificates or electronic birth files were obtained for cases and controls. Using identifying information on subjects collected from the hospital record, parents' names, Social Security numbers (when available), and years of birth were abstracted from the birth certificate. This information regarding subjects' parents was used to link them to employment and exposure data sources. Using site records, parental employment was determined for all subjects. Job history and exposure information was abstracted for those parents employed at the site. For employment ascertainment and exposure determination, subjects were not identified as to case or control status. A list of subjects' parents' names, including mother's name before marriage, Social Security numbers when available, and date or year of birth was developed from identifying information collected from hospital and vital records. This information was linked with the subject's estimated conception date, date of birth, and year of diagnosis to determine employment and exposure temporally relevant to disease diagnosis (onset).

The date of the subject's mother's last menstrual period (LMP), prior to the subject's birth, was collected from the birth certificate to determine the subject's date of conception. If LMP date was not on the birth certificate, it was abstracted from the prenatal record. If no LMP date was found, then the date of conception was calculated from gestational age at delivery or from the expected date of delivery recorded on the prenatal record. Date of conception is estimated by adding 14 days to the date of the LMP.

Once cases were identified and controls were selected using birth certificate information, and residence at diagnosis (index) year verified, the newborn record and the maternal delivery records were requested at the hospital of birth. These records were reviewed and abstracted to obtain information regarding pregnancy, delivery and characteristics of the newborn. If the

medical records were not available, or if some of the information was missing, the medical/demographic portion of the birth certificate was reviewed to obtain the information. Data obtained from the maternal record included information on parity, date of LMP, initiation of prenatal care, viral infections during pregnancy, and x-rays during pregnancy. Data regarding delivery included breach or other malpresentation and clinical estimation of gestational age. Information from the newborn record included plurality, birth weight and the presence and/or type of congenital malformations.

Following the ascertainment of cases, selection of controls, and the collection of parental identifiers from the birth certificate (and hospital record), the subjects' parents were linked to the employment rosters for the study sites, using names, Social Security numbers if available, and ages or dates of birth. These linkages were performed blindly with respect to the subjects' case or control status. The process used was slightly different for each site, as described below.

Computerized worker rosters for Hanford were obtained from the Epidemiology and Biometry Section of the Health Risk Assessment Department of Pacific Northwest Laboratory. These records were then searched by Battelle SRA staff -- using a standard linkage protocol and the date of conception to determine those subjects with a parent employed at the site at any time prior to the subject's conception. For those parents employed at Hanford, work history information was collected from worker files by Pacific Northwest Laboratory staff. The work histories covered the period prior to conception, during gestation, and up until time of diagnosis.

Determination of employment for INEL was more complex. Employment data have been collected by NIOSH as part of a cohort mortality study. Lists of subjects' parents' names were sent to NIOSH where they were soundex-matched to INEL employment rosters. The lists of

soundex-matched names were then sent to Battelle SRA where the names and additional information, such as Social Security numbers and ages, were compared with the soundex lists to identify matches. For many subjects from INEL no useful job history information was available; the only information consisted of hire and termination dates and the employing contractor.

For Oak Ridge, cases and pools of potential controls identified by ORAU and the Tennessee Department of Health were reviewed by Battelle SRA. Subjects who met the qualifying criteria were then matched against Oak Ridge employment rosters by ORAU staff.

Exposure Assessment

The primary hypothesis addressed in this study was whether there is an association between paternal preconception occupational radiation exposure and risk of developing childhood cancers. Information on paternal preconception radiation exposure was obtained from the dosimetric records for workers from the nuclear facilities. When subjects' fathers were identified as employees at the sites prior to conception, information was obtained on their radiation exposure prior to the subject's conception. The date of conception was estimated as described earlier. Dosimetric records were searched to determine all exposures prior to this date. When available, information was obtained on external whole-body penetrating radiation -- deep dose, neutron, and tritium doses.

Although dose information when possible was obtained for monthly periods, usually the data were cumulative by year. In this case doses received during the year of conception were assumed to have been distributed evenly over the year and yearly totals were divided by 12 to

get estimates of monthly exposure. These monthly estimates were then multiplied by the number of months that had elapsed in the year up to the estimated date of conception.

Paternal radiation doses were determined for the entire period of employment prior to conception. While it has been suggested, because of the timing of the sperm cycle, that exposures during the 3-6 months prior to conception might be the most biologically meaningful, data for most fathers were limited to annual doses. Attempts to obtain more time-limited dosimetric data were not rewarding. It can also be argued that if an effect is through stem-cell mutation then the timing of exposure is less important. In the Gardner et al. (1990b) study total cumulative doses and doses 6 months prior to conception were examined.

The dose estimates, expressed in millisieverts (mSv), were obtained from measurements made by personal dosimeters worn by employees. While there have been important technologic changes in dosimetry over the time span covered by the study, and there are differences among the sites in exposure (dose) assessment, the fact that the cases and controls were matched by year of birth and came from the same site makes the dosimetric methods comparable for both groups of subjects. All dosimetric data were assessed blindly with respect to the subject's case or control status. The quality of dosimetry for Hanford and Oak Ridge has been evaluated extensively in connection with mortality studies of workers at those two sites (Gilbert, Fix, and Baumgartner, 1990; Cardis et al., 1995).

For those subjects whose mothers were employed at the site we also obtained their dosimetric records. For maternal doses we determined both cumulative dose to conception and dose during gestation. Partioning of yearly doses to get monthly doses for both preconception and gestation was done using the same methods as described for paternal exposures.

We also obtained information on internal radionuclide depositions. Only a small number of workers at these three sites have had such depositions. At the Y-12 Oak Ridge facility, uranium exposure is of concern. For Hanford and ORNL, the doses are primarily external with limited potential for internal exposure.

In addition to radiation exposure we were interested in assessing other workplace exposures. Work histories and job titles were obtained from the site records. Unfortunately this information was often fragmentary, particularly for INEL. In addition, attempts to identify industrial hygiene records which could be used to estimate specific exposures were largely unsuccessful. Thus, although we obtained work histories and job titles when possible, we have not attempted to utilize those data. The complexity of the work environments in these sites would require a tremendous level of effort to reconstruct non-radiologic exposures in any meaningful way for Hanford and Oak Ridge and would seem to be impossible for INEL.

Statistical Methods

The data were analyzed using conditional regression implemented with the PECAN module of the software package EPICURE. The matching used to select controls was retained in the analyses, and reported analyses included single independent variables indicating either employment status or dose of one of the parents. Analyses of employment of the father or mother at the facility of interest prior to conception (EPC[1]) included all cases and all unrestricted controls. Analyses of the occupational doses of the parents included cases with

[1]The designation EPC is used as an abbreviation for "employed at the facility of interest prior to conception."

fathers who were EPC, restricted controls who were required to have EPC fathers, and unrestricted controls associated with the EPC cases who turned out to have EPC fathers. Fathers who were EPC but had not been monitored for external radiation exposure were assumed to have doses of zero. For two Hanford cases with EPC fathers, restricted controls had not been selected; these cases were placed in the matched sets of other cases that were very similar with respect to the matching criteria.

Because restricted controls were not selected for mothers who were EPC unless the father was also EPC, analyses addressing exposure of the mother or of both parents included only cases and matched controls where the father was also EPC; doses of mothers who were not EPC were assumed to be zero in these analyses. There were 4 cases with mothers EPC but without restricted controls; only one of these mothers had a positive dose prior to conception (1.44 mSv).

Odds ratios for the EPC status of fathers and mothers and for categories of paternal radiation dose were calculated. For EPC status, confidence intervals were based on the standard error for ß, where the odds ratio is of the form exp(ß). Because the data in the higher categories of paternal dose were sparse (with zero cases in several instances), confidence intervals for these odds ratios were based on the likelihood ratio statistic. Analyses with radiation dose treated as a continuous variable were also conducted. These included tests of the null hypothesis based on the score statistic, and estimation of the coefficients ß in either an exponential model of the form exp(ßz) or a linear model of the form 1 + ßz, where z was the paternal dose prior to conception with confidence intervals for ß based on the likelihood ratio statistic.

The exposure measure emphasized was the dose prior to conception, which was calculated as the cumulative dose up to the year of the estimated conception date plus a fractional part of the annual dose in the year of conception. For mothers, the gestational doses were also evaluated, and were calculated as described above.

Separate analyses were carried out for leukemia plus non-Hodgkin's lymphoma (NHL), leukemia alone, cancers of the central nervous system (CNS), and for the combined category of all childhood cancers (leukemia plus NHL plus CNS). For EPC status, separate analyses were carried out for Hanford, INEL, and Oak Ridge. Analyses of parental radiation dose were carried out for Hanford and for the combined data; the limited number of subjects with EPC parents at Idaho and Oak Ridge precluded separate analyses of data on parental dose from these facilities.

RESULTS

A total of 233 children who met the case definitions for this study was identified using the case ascertainment methods described above. The distribution of these cases by diagnosis and DOE site is shown in Table 1. Fathers of 28 of these cases were identified as being employed at one of the DOE study sites prior to the child's conception. A total of 104 restricted controls was selected for these cases: 60 for Hanford, 12 for INEL, and 32 for Oak Ridge. The ages of the cases at diagnosis are shown in Table 2.

The unrestricted control group included controls whose fathers were employed at the nuclear site. Information on the employment of case and unrestricted control fathers by DOE

site and diagnosis is shown in Table 3. This allowed us to calculate the odds ratios for case versus control fathers being employed at the sites.

Since most of the odds ratios shown in Tables 4-7 are less than unity, and all the confidence intervals include unity, overall, these results provide little evidence of an association of childhood cancer risk and paternal preconception employment at one of the DOE sites. Data for Hanford, Table 4, show that the proportion of leukemia and non-Hodgkin's lymphoma cases born to Hanford employees is virtually identical to that for unrestricted controls. Data for the three sites combined are similar to those of Hanford for leukemia and non-Hodgkins' lymphoma alone (Table 7). The odds ratio for central nervous system cancers at Hanford is elevated (2.50) but the lower limit of the 95% interval is less than 1.0 (0.79), but low odds ratios for the other two sites lead to an odds ratio for the combined data of 0.77 (Table 7).

Comparable data are shown for maternal preconception employment in Tables 8-11. As with paternal employment, there are no statistically significant associations between maternal preconception employment and cancer risk. The odds ratios for central nervous system cancers at Hanford and for the three sites combined are increased but in both instances the lower limit of the 95% confidence interval is less than 1.0 (Hanford OR=2.57, 95% CI=0.67 - 9.83; combined sites OR=2.75, 95% CI=0.85-8.91). All four Hanford central nervous system cases with mothers employed prior to conception also had fathers who were employed prior to conception. The OR for maternal employment at Oak Ridge could not be calculated because the two controls with mothers employed at Oak Ridge facilities were in different matched sets from the two cases with mothers so employed; thus the combined results in Table 11 are strongly driven by the Hanford data.

Analyses (not shown) were carried out of potential confounders such as number of prior live births, birth weight and maternal age. Such analyses were conducted for the combined category of all cancers at all three sites, and also for CNS for the Hanford site. These variables were not related to case status and their inclusion did not modify the results of analyses of employment prior to conception or of preconception dose so the odds ratios presented in the results section are unadjusted. Although information was collected from maternal and newborn records on other potential confounders, including viral illnesses and x-rays during pregnancy, plurality greater than one, malpresentation, and congenital malformations there were too few subjects with any of these conditions to conduct meaningful analyses.

Table 12 presents summary data on other exposure parameters for the subjects from the three sites for all cancers combined. A much higher percentage of subjects at INEL and Oak ridge had internal depositions than at Hanford; however it is possible that the criteria for deciding that a subject has such a deposition differed for the three sites. Note that very few subjects had positive neutron or tritium doses (all were at Hanford), and these were very small. There is no suggestion of an association of any of these exposure parameters with case status. This is further illustrated in Table 13 where the results of a score test for the three sites and the three cancer types combined are presented. With dose treated as a continuous variable there was no statistically significant association with father's dose prior to conception, mother's dose prior to conception, total parental dose prior to conception, mother's dose during gestation, or if the father had an internal deposition prior to conception.

Table 14 presents the distribution of subjects included in the dose-response analyses for each site and all sites combined for all cancers combined. Note that for each of the three DOE

sites the mean doses for the cases is less than the mean doses for the controls. As can be seen from this table, Hanford contributes most of the information to these analyses.

Table 15 shows the distribution of subjects by fathers' preconception doses from the three sites combined by cancer type, dose category, and case or control status. For each of the cancer types and for all cancers combined the mean preconception dose is lower for the cases than for the controls. There were no CNS cases with paternal doses exceeding 50 mSv.

In Table 16, the categorical analyses for paternal preconception dose are presented by cancer type. These analyses are restricted to the three sites combined because of the small numbers of subjects. When odds ratios are calculated relative to the 0-0.99 mSv category there are no odds ratios where the lower limit of the 95% confidence interval does not include 1.0. Because of the very small numbers of subjects in the dose categories above 50 mSv the confidence intervals are very wide.

Table 17 presents the estimates of the relative risks (RR) for all four case categories as a result of a paternal conception dose of 100 mSv based on a linear model. Table 17 shows estimates (with 95% confidence intervals) of the relative risk at 100 mSv for the combined data and for the Hanford data separately. These analyses treat the paternal dose received during the period prior to conception as a continuous variable, and the estimates are based on fitting the linear relative risk model. That is, the estimated relative risks were obtained as $1 + 100\ \beta$. Because the numbers of cases for INEL and Oak Ridge are small, the estimates are provided for Hanford alone and the three sites combined. These estimates do not show an increase in the relative risk that approaches statistical significance for any of the cancer types for the three sites combined. In all cases, the confidence intervals included unity, and, in most cases, the relative

risk was estimated to be less than one; in these cases, the lower confidence limits were not calculated. An increase is shown for leukemia at Hanford but the increase is not statistically significant (RR 1.93, 95% CI=<0.1-29) and the confidence interval is very wide due to the small sample size.

DISCUSSION

Summary

The results presented above do not support the primary study hypothesis of an association between paternal preconception radiation exposure and risk of leukemia, non-Hodgkin's lymphoma, central nervous system cancers, or all these cancers combined. Because of small sample sizes, the confidence intervals were wide, but in all cases included unity.

The findings are similar with respect to paternal employment at one of the DOE sites studied. Based on the distribution of paternal employment among the cases and the unrestricted controls, with one exception, the odds ratios do not support associations between employment and risk, similarly for maternal employment.

The findings regarding employment that are of some interest are similar odds ratios for paternal (OR 2.50, 95% CI 0.79-7.96) and maternal (OR 2.57, 95% CI 0.67-9.83) employment at Hanford and central nervous system cancer risk. The fact that the odds ratios are so similar, although both sets of confidence intervals include unity, suggests that this is a topic that may deserve further study in other populations of nuclear workers.

Limitations

In the conduct of this study we encountered a number of problems with the completeness and accuracy of the databases. It is important to note that some of the worker databases that were used have not been used for epidemiologic studies in the past. This is true, for example, for the databases for INEL. These databases were being assembled as the current study was underway. This applies not only to worker rosters but to dosimetry data as well.

Another limitation of the data has to do with their inadequacy for determining non-radiologic exposures. Our initial intent had been to try to use work histories to determine exposures to chemical or non-radiologic physical agents in the workplace. Review of records showed that job titles were complex, as different contractors used different titles. Titles and responsibilities also changed over time and were highly variable by location and building. It would have been extremely difficult to characterize what agents workers were exposed to in which buildings over time. In addition, hire and termination dates were sometimes missing. For these and other reasons that relate to the complexity of each site, the inclusion of three sites, and the time depth of the study, it was not possible to carry out that kind of assessment within the time frame of the study.

With regard to dosimetric data, while there is variability in the dosimetry methods over time and between sites the fact that the cases and controls were from the same site and were contemporaneous reduces the potential problems associated with this variability. With respect to missing dosimetry records, there is no reason to believe that these would bias the study in any way. Unmonitored workers, who account for most of the missing values, are usually workers who were thought to have little or no probability of exposure.

In addition to problems with employment records we encountered problems in obtaining birth records for cases and controls. While we received high levels of cooperation from many of the hospitals that provided us with access to records, charts were often missing and data were incomplete. This is not an unusual situation in large medical records-based data collection efforts, especially when a number of years have passed since the event of interest and numerous facilities are involved. Since these problems were mainly with newborn records there is no reason to believe that they affected cases and controls differently.

In addition to studying the individual types of cancer we also analyzed all the cancers together, given the lack of strong biologic hypotheses which would suggest differing etiologic mechanisms. Although no formal tests of heterogeneity between cancer types were conducted, the fact that all confidence intervals overlap, and include unity, indicates that whatever heterogeneity might have been present was not large enough to be detected statistically.

Comparison with Results from Other Studies

As noted earlier, Gardner et al. (1990a) reported a relative risk of about 6 for leukemia (also for the leukemia plus NHL) for fathers with preconception doses of 100 mSv or greater. In our study, the odds ratio for that category was 0.0 based on no cases and four controls among fathers with preconception doses at this level; upper limits of the 95% confidence intervals for the odds ratios associated with this dose level were 8.3 for leukemia, 4.4 for leukemia plus NHL, and 2.8 for all cancers. However, the estimated ORs for the 50+ mSv category, where one leukemia case occurred, were 1.7, 1.2 and 0.5 for the three respective cancers, and, although none of these ORs were significantly elevated, the upper confidence limits were

somewhat larger than for the 100+ mSv category . Although these results clearly do not provide additional support for the correlation identified by Gardner et al. (1990a), the small number of cases and controls with doses at the level where the Gardner effect was seen make it difficult to draw firm conclusions regarding compatibility of our findings and those of Gardner.

A more powerful analysis is obtained by analyzing dose as a continuous variable, as shown in Table 17. Although Gardner et al. (1990a) did not present dose-response analyses, Little, Charles and Wakeford (1995) show results of such analyses based on a further study of childhood cancer in West Cumbria conducted the U.K. Health and Safety Executive (HSE 1993). This study, which includes more up-to-date case data and some refinement of dose estimates over the those used by Gardner et al, found a significant association between cumulative paternal preconception irradiation and the category of leukemia and non-Hodgkin's lymphoma when dose was treated as a continuous variable (HSE 1993). This association was however limited to offspring of the Sellafield workforce who were born in Seascale. The results for the Seascale and non-Seascale components of this study are shown in Table 18, and are based on a comparable approach to our continuous analyses (Table 17). Little, Wakeford and Charles (1994) also present results for other studies (calculated from published data from these studies), which are shown in Table 18.

Little, Wakeford and Charles (1994) note that the relative risks associated with paternal preconception exposure for offspring of Sellafield workers born in Seascale differed (with a high level of statistical significance) from those in the Japanese, Ontario, and Scottish data sets, as well as from those in offspring of Sellafield workers born outside Seascale. Thus there is a

highly significant discrepancy between the Seascale children and the other data. Importantly, for these other populations, the upper limit of the confidence interval is lower than the relative risk (odds ratio) for the Seascale worker population. With the exception of Seascale, the confidence limits indicate compatibility both with no excess risk resulting from paternal exposure and with relative risks of about 2 or 3 for a worker with a 100 mSv exposure (although the upper limit from the A-bomb survivor study is only 1.2).

The results of analyses with dose as a continuous variable, based on the U.S. worker data (Table 17), are clearly compatible with all of the non-Seascale results. The U.S. results based on the combined data for all cancers and for leukemia plus NHL, where the upper limits of the 95% confidence intervals are respectively 2.1 and 3.5 for a 100 mSv exposure, are incompatible with the Seascale result. A limitation of our data, and data from other worker studies, is that data are sparse at higher doses, and thus these studies have low power that results in wide confidence intervals. Although the studies (other than Seascale) are compatible with no risk, they are also compatible with levels of risk that exceed the upper limit of the 95% confidence interval based on the Japanese A-bomb survivors.

CONCLUSION

The results of this study, for all the cancer types combined, for leukemia and lymphoma, both for individual DOE facilities and for the three facilities combined, are consistent with a null hypothesis of no association between paternal preconception exposure and risk of these forms of childhood cancer. Thus, our findings do not support the earlier association observed by Gardner et al. (1990a) for Sellafield. The findings are consistent with subsequent studies that

have failed to demonstrate (observe) increased risks associated with preconception doses of radiation received by fathers employed by nuclear facilities. It is our interpretation of these results and the accumulating scientific evidence that there do not appear to be increased risks of leukemia and non-Hodgkin's lymphoma among children whose fathers have been occupationally exposed to ionizing radiation at currently acceptable levels.

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Table 1
Numbers of Cases by Diagnosis by DOE Site

	DOE Site			
Diagnosis	Hanford	INEL	Oak Ridge	All Sites
Leukemia	30	39	63	132
Non-Hodgkin's Lymphoma	4	8	14	26
Central Nervous System	20	15	40	75

Table 2
Cases by Age at Diagnosis by Diagnosis, All Sites Combined

	Age				
Diagnosis	<1	1-5	6-10	>10-15	Total
Leukemia	15	61	33	22	131
Non-Hodgkin's Lymphoma	1	9	6	10	26
Leukemia and Lymphoma	0	1	0	0	1
CNS	7	34	21	13	75

Table 3
Numbers of Cases and Unrestricted Controls Whose Fathers Were Employed at the DOE Sites Prior to Their Conception, by Diagnosis by DOE Site

Diagnosis	Hanford		INEL		Oak Ridge		All Sites	
	Cases	Unrestricted Controls	Cases	Unrestricted Controls	Cases	Unrestricted Controls	Cases	Unrestricted Controls
Leukemia	6	26	2	9	6	26	14	61
Non-Hodgkin's Lymphoma	1	7	0	5	1	9	2	21
Central Nervous System	10	26	1	8	1	19	12	53

Table 4
Employment of Fathers of Cases and Unrestricted Controls Prior to Conception at Hanford by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	30	34	20	54
Father EPC	6	7	10	17
Proportion	0.20	0.21	0.50	0.31
Total unrestricted controls	120	136	80	216
Father EPC	26	33	26	59
Proportion	0.22	0.24	0.33	0.27
Odds Ratio (95% CI)	0.90 (0.32-2.53)	0.79 (0.30-2.08)	2.50 (0.79-7.96)	1.27 (0.63-2.56)

Table 5
Employment of Fathers of Cases and Unrestricted Controls Prior to Conception at Idaho National Engineering Laboratory by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	39	47	15	62
Father EPC	2	2	1	3
Proportion	0.051	0.043	0.067	0.048
Total unrestricted controls	156	188	60	248
Father EPC	9	14	8	22
Proportion	0.058	0.075	0.13	0.089
Odds Ratio	0.87	0.52	0.43	0.49
(95% CI)	(0.16-4.67)	(0.11-2.53)	(0.05-4.05)	(0.13-1.78)

Table 6
Employment of Fathers of Cases and Unrestricted Controls Prior to Conception at Oak Ridge by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	63	77	40	117
Father EPC	6	7	1	8
Proportion	0.095	0.091	0.025	0.068
Total unrestricted controls	252	308	160	468
Father EPC	26	35	19	54
Proportion	0.10	0.11	0.12	0.12
Odds Ratio (95% CI)	0.90 (0.34-2.44)	0.76 (0.31-1.86)	0.15 (0.018-1.31)	0.53 (0.23-1.19)

Table 7
Employment of Fathers of Cases and Unrestricted Controls Prior to Conception at Three Sites Combined by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	132	158	75	233
Father EPC	14	16	12	28
Proportion	0.11	0.10	0.16	0.12
Total unrestricted controls	528	632	300	932
Father EPC	61	82	53	135
Proportion	0.12	0.13	0.18	0.14
Odds Ratio	0.90	0.73	0.86	0.77
(95% CI)	(0.46-1.73)	(0.40-1.33)	(0.40-1.85)	(0.48-1.24)

Table 8
Employment of Mothers of Cases and Unrestricted Controls Prior to Conception at Hanford by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	30	34	20	54
Mother EPC	0	0	4	4
Proportion	0.00	0.00	0.20	0.074
Total unrestricted controls	120	136	80	216
Mother EPC	9	10	7	17
Proportion	0.075	0.074	0.088	0.079
Odds Ratio (95% CI)	0.00	0.00	2.57 (0.67-9.83)	0.94 (0.30-2.90)

Table 9
Employment of Mothers of Cases and Unrestricted Controls Prior to Conception at Idaho National Engineering Laboratory by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	39	47	15	62
Mother EPC	2	2	0	2
Proportion	0.051	0.043	0.00	0.032
Total unrestricted controls	156	188	60	248
Mother EPC	6	8	2	10
Proportion	0.039	0.043	0.033	0.040
Odds Ratio (95% CI)	1.33 (0.27-6.61)	1.00 (0.21-4.71)	0.00	0.79 (0.17-3.72)

Table 10
Employment of Mothers of Cases and Unrestricted Controls Prior to Conception at Oak Ridge by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	63	77	40	117
Mother EPC	2	2	2	4
Proportion	0.032	0.026	0.050	0.034
Total unrestricted controls	252	308	160	468
Mother EPC	8	8	2	10
Proportion	0.024	0.026	0.013	0.021
Odds Ratio (95% CI)	1.00 (0.19-5.37)	1.00 (0.19-5.37)	Undefined	1.88 (0.47-7.44)

Table 11
Employment of Mothers of Cases and Unrestricted Controls Prior to Conception at Three Sites Combined by Diagnosis

Employment	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All
Total cases	132	158	75	233
Mother EPC	4	4	6	10
Proportion	0.030	0.025	0.080	0.043
Total unrestricted controls	528	632	300	932
Mother EPC	23	26	11	37
Proportion	0.044	0.041	0.037	0.040
Odds Ratio (95% CI)	0.68 (0.23-2.02)	0.60 (0.20-1.76)	2.75 (0.85-8.91)	1.09 (0.52-2.29)

Table 12
Summary Data on Other Radiologic Exposures for Cases and Controls Included in Dose-Response Analyses for All Three Diagnoses by DOE Site

Diagnosis	Hanford		INEL		Oak Ridge		All Sites	
	Cases	Unrestricted Controls	Cases	Unrestricted Controls	Cases	Unrestricted Controls	Cases	Unrestricted Controls
Number of fathers with internal depositions	1	2	1	6	2	12	4	20
Number of fathers with positive neutron dose (max.)	0	7 (11mSv)	0	1 (0.4 mSv)	0	0	0	8 (11 mSv)
Number of fathers with positive tritium dose	0	1 (0.05 mSv)	0	0	0	0	0	1 (0.05 mSv)
Number with positive maternal doses prior to conception (max.)	3 (9.9 mSv)	13 (11 mSv)	0	0	1 (1.9 mSv)	0	4 (10 mSv)	13 (11 mSv)
Number with positive maternal doses during gestation (max.)	2 (2.2 mSv)	4 (1.4 mSv)	0	0	0	0	2 (2.2 mSv)	4 (1.4 mSv)

Table 13
Assessment of Relationship of Several Dose Measures to All Cancers
(Dose Treated as Continuous Variable)

Dose Measures	Score Test (One-tailed p-Value)	
	Hanford	Three Study Sites Combined
Father's dose prior to conception	-0.58 (0.72)	-0.91 (0.82)
Mother's dose prior to conception	0.65 (0.26)	0.89 (0.19)
Mother's dose during gestation	1.50 (0.067)	1.50 (0.067)
Total parental dose prior to conception	-0.55 (0.71)	-0.88 (0.81)
Father had internal deposition prior to conception	0.83 (0.20)	-0.88 (0.81)

Table 14
Distribution of Subjects Included in Dose-Response Analyses by Total Dose Received by the Father Prior to Conception -- All Cancers

Dose category	Site							
	Hanford		Idaho		Oak Ridge		All Sites Combined	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0	1	7	2	7	5 (4[a])	25 (20)	8 (4)	39 (20)
0, <1	6	19	1	0	2	5	9	24
1-	7	38	0	2	1	5	8	45
10-	2	16	0	1	0	0	2	17
50-	1	1	0	2	0	1	1	4
100+	0	3	0	0	0	1	0	4
Total	17	84	3	12	8	37	28	133
Mean dose[b] (mSv)	7.1	14.4	0.16	15.1	0.26	5.4	4.4	12.0

[a]Number of unmonitored cases or controls. For Hanford unmonitored could not be distinguished from recorded doses of zero.
[b]Unmonitored cases and controls were assumed to have doses of zero.

Table 15
Distribution of Cases and Controls by Total Dose Received by the Father Prior to Conception by Diagnosis for the Three Study Sites Combined

Dose category	Diagnosis							
	Leukemia		Leukemia and NHL		CNS		All Cancers	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0	5 (3[a])	29 (14)	5 (3)	31 (16)	3 (1)	8 (4)	8 (4)	39 (20)
0, <1	5	11	6	14	3	10	9	24
1-	3	13	4	15	4	30	8	45
10-	0	7	0	9	2	8	2	17
50-	1	1	1	1	0	3	1	4
100+	0	2	0	3	0	1	0	4
Total	14	63	16	73	12	60	28	133
Mean dose[b] (mSv)	5.4	8.0	5.0	13.3	3.6	10.3	4.4	12.0

[a]Number of unmonitored cases or controls. For Hanford unmonitored could not be distinguished from recorded doses of zero.
[b]Unmonitored cases and controls were assumed to have doses of zero.

Table 16
Odds Ratios and 95% Confidence Interval for Categorical Analyses of Dose Received by the Father Prior to Conception for the Three Study Sites Combined

	Diagnosis			
Dose Category (mSv)	Leukemia	Leukemia and NHL	CNS	All Cancers
0-.99	1.00	1.00	1.00	1.00
1-49.99	0.51 (0.10-2.1)*	0.60 (0.15-2.1)	0.43 (0.081-2.0)	0.54 (0.19-1.4)
50-99.99	5.02 (0.20-126)	5.10 (0.20-129)	0.00 (0.0-2.9)	0.95 (0.045-8.2)
100+	0.00 (0.0-8.3)	0.00 (0.0-4.4)	0.00 (0.0-16)	0.00 (0.0-2.8)
50+	1.69 (0.081-14)	1.24 (0.062-8.8)	0.00 (0.0-2.1)	0.48 (0.025-3.2)

*95% Confidence Interval

Table 17
Estimates of Relative Risk and 95% Confidence Intervals for Study Childhood Cancers as a Result of a Dose of 100 mSv Received by the Father Prior to Conception for Hanford and the Three Study Sites Combined Based on a Linear Model OR=1+ß Dose

DOE Site	Diagnosis			
	Leukemia	Leukemia and NHL	CNS	All Cancers
Combined	0.73 (<0.73-7.6)*	0.75 (<0.75-3.5)	0.22 (<0.22-3.6)	0.75 (<0.75-2.1)
Hanford	1.93 (<0.1-29)	0.75 (<0.75-6.5)	0.22 (<0.22-8.1)	0.75 (<0.75-3.3)

*95% Confidence Interval

Table 18
Estimated Relative Risks of Childhood Leukemia and Non-Hodgkin's Lymphoma Associated with a Preconception Paternal Dose of 100 mSv Based on a Linear Model (Little, Wakeford and Charles 1994)

Population	Relative Risk (95% CI)
Sellafield (Seascale)	+ ∞ (3.96 - ∞)
Sellafield (remainder)	0.73 (0.47-2.08)
Scotland	<0.51 (<0.51-2.95)
Ontario	0.63 (<0.27-3.40)
Scotland and Ontario	0.55 (<0.51-2.15)
A-bomb survivors	1.01 (<0.99-1.19)