Paternal occupation as a risk factor for leukaemia and Non-Hodgkin lymphoma in children and young adults.  
A study from the North of England.

Donna M Hammal, Mark S Pearce, M Tevfik Dorak, and Louise Parker.

Paediatric and Lifecourse Epidemiology Research Group, School of Clinical Medical Sciences, 
University of Newcastle upon Tyne, RVI, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP, UK 
Tel: +44 (0) 191 2023032; Fax: +44 (0) 191 2023060; E-mail: D.M.Hammal@ncl.ac.uk

Summary

Data from the Northern Region Young Persons’ Malignant Disease Registry were used to investigate the role that paternal occupation at birth may have in the aetiology of leukaemia and Non-Hodgkin’s lymphoma in children and young adults. Paternal occupation at birth was available for 2321 children (0-14 years at diagnosis) and for 2413 young adults (15-24 years), constituting 90% of registered cases. An occupational exposure matrix was constructed to test paternal exposure groups previously associated with childhood cancer. For each disease type, conditional logistic regression was used to test if the risk of disease was associated with each of these exposure groups by comparing cases with two independent sets of controls, matched on gender and year of birth, drawn from the other cases in the cancer registry and from the Cumbrian Births Database.

There was a statistically significant increased risk of ALL for paternal occupations in the radiation and electromagnetic field group compared to both control groups in children aged 1-6 years at diagnosis (OR 1.68, 95% CI 1.17-2.41 and OR 1.69, 95% CI 1.18-2.43, compared to registry and Cumbrian controls respectively). These associations were almost identical after controlling for social class, and after excluding the offspring of fathers employed at the Sellafield nuclear installation. Children of fathers occupationally exposed to pesticides and herbicides were at a lower risk of ALL (OR 0.48, 95% CI 0.28-0.82 and OR 0.25, 95% CI 0.12-0.52) in those aged 1-6 years and 7-24 years, respectively. Additionally those aged 7-24 years were at a reduced risk of AnLL and NHL (OR 0.32, 95% CI 0.13-0.79 and OR 0.20, 95% CI 0.08-0.55, respectively). However, these results were confined to the analysis using non-registry controls, which may be due to confounding from rural occupations.

These results suggest that further detailed investigation into the role of paternal electromagnetic field exposure, paternal pesticide/herbicide exposure and predominantly rural occupations, in these cancers in children and young adults is required.

Introduction

Numerous studies have implied that paternal occupational exposures may have a role in the aetiology of childhood cancers (Little, 1999). In particular, occupations with exposures to radiation (Gardner et al. 1990), electromagnetic fields (EMF) (Smulevich et al. 1999; Feychting et al. 2000), pesticides/herbicides (Zahm and Ward, 1998; Meinert et al. 2000) have been associated with specific childhood cancers, though some of these findings have been challenged (Pearce and Parker, 2000).

We therefore tested the hypothesis that an association exists between paternal occupations at the time of birth and cancer risk in children and young adults in the North of England, using data from the Northern Region Young Persons’ Malignant Disease Registry (NRYPMDR) ( Cotterill et al. 2000). The NRYPMDR is a population based registry recording young people, aged under 25 years, diagnosed with malignancies, resident in the North of England since 1968 (Cotterill et al. 2000).

Materials and Methods

Case-control analyses were undertaken for leukaemia and non-Hodgkin’s lymphoma (NHL) in the 0, 1-6 and 7-24 years age groups. Analyses with small case numbers were not reported (hence results from the 0 years age group have been omitted). Odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated using conditional logistic regression.

Study Subjects

We ascertained from the NRYPMDR cases of primary leukaemia and lymphoma, diagnosed between 1968 and 2000. Tumours were coded for morphology and site using the International Classification of Diseases for Oncology (ICDO-2) (Percy et al. 1990).

Two independent sets of controls were selected. Firstly, for each particular disease group all other patients from the NRYPMDR with different disease types, with the same gender and year of
birth as each case, were selected as controls. Secondly, 100 cancer-free controls were randomly selected from live births recorded on the Cumbrian Births Database (CBD), again matched on gender and year of birth. The CBD holds birth registration details on all children born to mothers resident in the county of Cumbria, in the North of England, between 1950 and 1993 (Parker et al. 1997). In common with the rest of the study region, Cumbria is a mixture of both urban and rural areas, but is among the most sparsely populated counties in England, with industrial areas, including the Sellafield nuclear installation, concentrated in the south-west.

**Paternal occupation**

Paternal occupation, as recorded on birth certificates, was obtained and coded according to the 1990 Standard Occupational Classification (OPCS, 1990) with social class (I (professional), II, III non-manual, III manual, IV, V) being subsequently derived. Those for whom paternal occupation was unavailable from birth certificates or for which there was no suitable occupational code (including “unemployed” and “student”) were excluded. We designed an exposure matrix based on the occupational classification system for the pre-specified occupational groups of interest (Table 1).

**Table 1. Exposure matrix for paternal occupations**

<table>
<thead>
<tr>
<th>Occupational Group</th>
<th>Standard Occupational Classification codes (OPCS, 1990)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation / EMF</td>
<td>126, 202, 212-214, 302, 320, 330-331, 342, 450-452, 459, 463, 490, 520-529</td>
</tr>
</tbody>
</table>

**Results**

Paternal occupation at birth, was available for 4,734 case children and young adults (90% of registered cases). Results of the case-control analysis, along with subject numbers are in Table 2.

**Table 2. Odds ratios and corresponding 95% confidence intervals, for the radiation/emf and pesticide/herbicide occupation groups.**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Radiation/EMF</th>
<th>Registry controls</th>
<th>Cumbrian controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. cases</td>
<td>No. controls</td>
<td>OR</td>
</tr>
<tr>
<td>1-6</td>
<td>ALL ¹</td>
<td>414</td>
<td>16,026</td>
</tr>
<tr>
<td></td>
<td>AnLL ²</td>
<td>48</td>
<td>1,838</td>
</tr>
<tr>
<td></td>
<td>NHL ³</td>
<td>37</td>
<td>1,664</td>
</tr>
<tr>
<td>7-24</td>
<td>ALL</td>
<td>309</td>
<td>14,185</td>
</tr>
<tr>
<td></td>
<td>AnLL</td>
<td>144</td>
<td>6,659</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>204</td>
<td>9,743</td>
</tr>
<tr>
<td>Pest/Herb</td>
<td>ALL</td>
<td>414</td>
<td>16,026</td>
</tr>
<tr>
<td></td>
<td>AnLL</td>
<td>48</td>
<td>1,838</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>37</td>
<td>1,664</td>
</tr>
<tr>
<td>7-24</td>
<td>ALL</td>
<td>309</td>
<td>14,185</td>
</tr>
<tr>
<td></td>
<td>AnLL</td>
<td>144</td>
<td>6,659</td>
</tr>
<tr>
<td></td>
<td>NHL</td>
<td>204</td>
<td>9,743</td>
</tr>
</tbody>
</table>

¹ Acute lymphoid leukaemia  ² Acute non-lymphocytic leukaemia  ³ Non-Hodgkin’s lymphoma

**Radiation/EMF**

Children aged 1-6 years; of fathers in the radiation/EMF occupational group had a statistically significant elevated risk of ALL compared to both registry and Cumbrian controls (Table 3). Excluding cases with fathers who were employed at the Sellafield nuclear installation, in whom an excess of childhood leukaemia has been reported (Gardner et al. 1990), made little difference to these results (OR 1.83, 95% CI 1.26-2.67 and OR 1.82, 95% CI 1.25-2.64, respectively). Similarly, adjustment for paternal occupational social class did not vastly change results. Paternal occupation in this group was not associated with any of the other diagnostic groups.
**Pesticides/Herbicides**

Children whose fathers were occupationally exposed to pesticides/herbicides were found to have a reduced risk of lymphoid leukaemia, both for those aged 1-6 years and those aged 7-24 years, when compared to Cumbrian controls (Table 3). Reduced risks were also seen for acute non-lymphocytic leukaemia and non-Hodgkin lymphoma in this older age group, again only in the analysis using the Cumbrian controls. Adjustment for paternal occupational social class made little difference.

**Discussion**

This study examined the role of paternal occupation at birth on the risk of leukaemia and non-Hodgkin’s lymphoma in children and young adults. The occupations investigated were those with potential exposures previously implicated by a number of other studies (Little, 1999). Less is known about the role of paternal occupation at birth in cancers in young adults (15-24 years) (Bleyer, 2002).

The major strengths of this study are its size and population base. Over 4000 cases of cancer in children and young adults were included from the registry which is believed to be more than 95% complete (Cotterill et al. 2000). Our exposures of interest occurred in approximately 5% of the population studied; thus with a power of 80% and a significance level of 5%, we were able to detect a minimum risk of 1.7. Two large independent control groups were used in order to reduce bias and findings were broadly similar using the two control groups. Minimal bias in control selection should be expected in this study, unlike in some interview based studies. This study also has some limitations, many of which apply to most of the studies in this field; the use of job title as a surrogate for exposure, lack of data on levels or duration of exposure, possible changes in exposure within occupational groups over the long study period, and multiple testing could all potentially give rise to spurious results. There is also the possibility that other factors unavailable to this study, such as maternal occupational exposures or lifestyle factors in childhood or in early adult life, could explain the findings.

**Radiation/EMF**

There was an excess of children aged 1-6 years with ALL whose fathers had occupations associated with radiation/EMF exposures. This excess risk remained after the analysis was restricted to paternal occupations associated with predominantly EMF exposures. Similar results were found with both control groups. Our findings are consistent with a number of previous studies which also found significantly increased risks amongst the children of men occupationally exposed to electromagnetic fields (Smulevich et al. 1999; Feychting et al. 2000). Collectively, these studies suggest that further research into the role of paternal occupational exposures to EMF, in the aetiology of childhood leukaemia are warranted.

The potential mechanisms of risk are uncertain. It is not clear if paternal exposure to lower frequency non-ionising electromagnetic fields has direct preconceptional genomic effects. There is great variation in reports regarding the magnitude to which electricians are exposed to EMF, but doses are, generally, substantially higher than in most other occupations. Alternatively, the elevated risk seen in fathers employed in electrical related jobs at the time of birth could be confounded by preconceptional or lifetime “take-home” effects of other occupational exposures also linked with childhood leukaemia, such as solvents (Little, 1999), to which workers in these industries are frequently exposed. It is also possible that this group of workers is particularly mobile or involves a high degree of interpersonal contact which could increase the risk to their children of exposure to infections, which has been postulated to increase the risk of childhood leukaemia (Kinlen, 1995; Alexander et al. 1997; Greaves, 1997). A separate study of all paternal occupations involving contact with other individuals has recently been completed using the same data (Pearce et al. 2004). An increased risk of childhood leukaemia and non-Hodgkin’s lymphoma was seen for those children whose fathers’ occupational contacts were very high (OR 1.5, 95% CI 1.2-1.9).

**Pesticides/Herbicides**

This study found reduced risks of ALL in 1-6 year olds, and ALL, AnLL and NHL in 7-24 year olds in children and young adults whose fathers were exposed to pesticides/herbicides. Previous
studies examining the relationship between paternal occupational exposure to pesticides and the risk of childhood leukaemia have found increased rather than decreased risks (Infante-Rivard and Sinnett, 2001). In our study, the significantly decreased risks were restricted to the Cumbrian control group only. It is possible that this particular occupational exposure group acts as a surrogate for occupation in farming occupations, and that the reduced risks observed are a result of confounding with rural and farming occupations which, through the overall increase in early antigenic exposures, may result in reduced risks consistent with the hygiene hypothesis (Strachan, 1989). This needs further exploration.

Conclusion
These results suggest that further detailed investigations into the potential role of paternal occupational exposure around the time of birth on the risk of leukaemia in children and young adults are required.

Acknowledgement
We thank Lorna More for providing information from the Northern Region Young Persons’ Malignant Disease Registry. This study was funded by the North of England Children’s Cancer Research Fund.

References


