The relationship between parental occupation and bone cancer risk in offspring

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Background
Bone cancers in children are serious and highly fatal conditions, yet relatively little is known about their causes or methods of prevention.

Methods
The relationship between parental occupation and bone cancer in offspring was explored in a case-control study. Cases were identified from the Ontario Cancer Registry; population-based controls were matched on sex and age. Data were collected from their parents through the use of a mailed self-administered questionnaire.

Results
The odds ratio estimates (OR) for bone cancer were elevated for fathers in the social sciences (OR = 2.5, 95% confidence interval [CI] : 0.7-8.4). Risk of Ewing's sarcoma was significantly high among children with fathers in social sciences (OR = 6.2, 95% CI: 1.6-24.5) and mothers in teaching (OR = 3.1, 95% CI: 1.1-8.7) or farming (OR = 7.8, 95% CI: 1.9-31.7). Osteosarcoma risk was increased for fathers in farming (OR = 2.1, 95% CI: 0.8-5.7), and mothers in managerial and administrative work (OR = 2.3, 95% CI: 0.6-8.1), and product fabricating, assembling, and repairing (OR = 2.0, 95% CI: 0.6-7.2).

Conclusions
Certain methodological problems plague studies of bone cancer in children (e.g. small studies, low statistical power, analysis of multiple occupational categories, difficulty in identifying specific carcinogenic agents). These associations require further investigation, especially as elevated risks have been reported previously for agricultural occupations.

Keywords
Bone cancer, osteosarcoma, Ewing's sarcoma, parental occupation, case-control study

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overall response rate of 86% (271/317). Among respondents, 85 individuals were subsequently considered to be ineligible (74 of these identified subsequently by the Registry as having been diagnosed before 1980). Thus, a total of 186 responding cases were identified.

Population-based controls included Ontario residents who were randomly selected by telephone and matched to cases on sex and age (± 2 years). Two telephone selection procedures were used. The first involved random digit dialling from a list of valid Ontario area code-prefix combinations, excluding non-residential numbers and numbers known to be out of service, with the last four digits of the telephone number randomly generated. The second selection method was dialling from a list of randomly selected residential telephone numbers provided by Bell Canada. Controls had to have lived in Ontario during the same time as their matched case. A total of 1131 controls was assembled; among these, 919 questionnaires were returned, yielding an overall response rate of 81% among known, eligible controls.

Data were collected from self-administered questionnaires mailed during 1988–1990 to the mothers of cases and controls. Inquiries about parental employment included all occupations in which the parent had worked for 6 months or more, the associated industries or businesses, and the years of employment. Occupations were categorized according to the two-digit codes of the 1980 Standard Occupational Classification (SOC). 10 For each parent, 21 occupational categories were examined. If parents held jobs in two or more occupational categories, their exposure was considered in each of the categories in which they worked. The time period of interest for paternal occupation exposure was prior to, but excluding, the year of conception. For maternal occupation exposure, the time period of interest included the year of birth.

Subjects were excluded if the child was adopted or occupation or dates of employment were not specified. The data set for analysis included 152 cases (82%) and 713 controls (78%) for paternal occupation and 115 cases (62%) and 600 controls (65%) for maternal occupation.

Maximum likelihood estimates of the odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated for each occupational group by unconditional logistic regression, adjusted for sex and age. The association was evaluated for all bone cancer combined, and for osteosarcoma and Ewing’s sarcoma. Variables evaluated for potential confounding were maternal and paternal age at subject’s birth, subject exposure to x-rays, maternal exposure to x-rays during pregnancy, and occupation of the other parent. This latter was confined to that occupation which was the same as the index parent’s occupation. As there was no evidence of confounding, the OR were adjusted for sex and age only in the analyses presented.

Dose-response was assessed using length of employment, with the intensity of exposure assumed to be constant. For all analyses, the reference exposure category comprised subjects whose parent did not work in the job of interest, or whose parent worked in the occupation of interest but not during the relevant time period for exposure.

### Results

The distribution of paternal and maternal occupations is displayed by case-control status in Table 1. As no fathers or mothers had been employed in certain occupational categories, OR were estimated for 16 paternal and 9 maternal occupations. Table 2 displays the OR and corresponding 95% CI associated with each paternal and maternal occupation for all bone cancer types combined and for osteosarcoma and Ewing’s sarcoma. The results from the dose-response analysis are presented in Table 3.

### Paternal occupation

For all bone cancer types combined, an elevated OR was observed for paternal occupation in the social sciences (OR = 2.5, 95% CI : 0.7–8.4). Odds ratio estimates were elevated also

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Table 1 Distribution of paternal and maternal occupation by case-control status

<table>
<thead>
<tr>
<th>Occupation</th>
<th>Paternal Cases (%)</th>
<th>Controls (%)</th>
<th>Maternal Cases (%)</th>
<th>Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managerial, Administrative, and related</td>
<td>18 (11.3)</td>
<td>69 (9.7)</td>
<td>5 (4.3)</td>
<td>15 (2.5)</td>
</tr>
<tr>
<td>Natural Sciences, Engineering, and Math.</td>
<td>8 (5.3)</td>
<td>50 (7.0)</td>
<td>0</td>
<td>6 (1.0)</td>
</tr>
<tr>
<td>Social Sciences and related</td>
<td>4 (2.6)</td>
<td>8 (1.1)</td>
<td>0</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Teaching and related</td>
<td>7 (4.6)</td>
<td>26 (3.7)</td>
<td>13 (11.3)</td>
<td>32 (5.3)</td>
</tr>
<tr>
<td>Medicine and Health</td>
<td>3 (2.0)</td>
<td>9 (1.3)</td>
<td>14 (12.2)</td>
<td>51 (8.5)</td>
</tr>
<tr>
<td>Artistic, Literary, Recreational, and rel.</td>
<td>1 (0.7)</td>
<td>7 (1.0)</td>
<td>0</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Clerical and Related</td>
<td>8 (5.3)</td>
<td>24 (3.4)</td>
<td>26 (22.6)</td>
<td>147 (24.5)</td>
</tr>
<tr>
<td>Sales</td>
<td>5 (3.3)</td>
<td>50 (7.0)</td>
<td>4 (3.5)</td>
<td>25 (4.2)</td>
</tr>
<tr>
<td>Service</td>
<td>3 (2.0)</td>
<td>32 (4.5)</td>
<td>5 (4.3)</td>
<td>44 (7.3)</td>
</tr>
<tr>
<td>Farming, Horticultural, and Animal Husbandry</td>
<td>8 (5.3)</td>
<td>25 (3.5)</td>
<td>4 (3.5)</td>
<td>8 (1.3)</td>
</tr>
<tr>
<td>Mining and Quarrying</td>
<td>3 (2.0)</td>
<td>14 (2.0)</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Processing</td>
<td>5 (3.3)</td>
<td>26 (3.7)</td>
<td>2 (1.7)</td>
<td>13 (2.2)</td>
</tr>
<tr>
<td>Machining and related</td>
<td>4 (2.6)</td>
<td>19 (2.7)</td>
<td>0</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Product Fabricating, Assembling, and Repairing</td>
<td>13 (8.6)</td>
<td>63 (8.8)</td>
<td>5 (4.3)</td>
<td>17 (2.8)</td>
</tr>
<tr>
<td>Construction Trades</td>
<td>11 (7.2)</td>
<td>69 (9.7)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Transport Equipment Operating</td>
<td>6 (4.0)</td>
<td>40 (5.6)</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

* Percentage of total cases.

\(b\) Percentage of total controls.
for children of men ever employed in teaching (OR = 1.4, 95% CI: 0.6-3.3); medicine and health (OR = 1.6, 95% CI: 0.4-6.0); clerical work (OR = 1.5, 95% CI: 0.6-3.3); and farming, horticulture, and animal husbandry (OR = 1.4, 95% CI: 0.6-3.2). Conversely, the OR among children of men ever employed in service occupations was markedly lower than one (OR = 0.4, 95% CI: 0.1-1.5). None of these OR estimates was statistically significant.

An increased relative risk of osteosarcoma was observed among subjects whose fathers had ever been employed in farming, horticulture, and animal husbandry (OR = 2.1, 95% CI: 0.8-5.7). Other occupations which also presented somewhat elevated OR included: teaching (OR = 1.6, 95% CI: 0.5-4.6); managerial and administrative positions (OR = 1.5, 95% CI: 0.7-3.1); clerical work (OR = 1.7, 95% CI: 0.6-5.1); and machining (OR = 1.6, 95% CI: 0.5-5.5). The OR among children of men ever employed in sales was noticeably, but not statistically significantly, less than one (OR = 0.2, 95% CI: 0.0-1.4). The relative risk of Ewing’s sarcoma was significantly increased for children of fathers ever employed in the social sciences (OR = 6.2, 95% CI: 1.6-24.5), and was not significantly elevated for children of fathers ever employed in medicine and health (OR = 1.6, 95% CI: 0.2-12.9), and in managerial and administrative work (OR = 1.6, 95% CI: 0.7-3.8).

The relative risk estimate of bone cancer was somewhat elevated among subjects whose fathers had been employed in the social sciences <5 years (OR = 2.2, 95% CI: 0.5-9.1) or ≥5 years (OR = 3.0, 95% CI: 0.3-34.0) (Table 3). For some occupational categories, the relative risk of bone cancer was high only for subjects whose fathers had worked ≥5 years: farming, horticulture, and animal husbandry (OR = 2.4, 95% CI: 0.9-6.4); and clerical (OR = 2.6, 95% CI: 0.6-11.0). Conversely, subjects whose fathers worked 1-4 years in occupations in the natural sciences, engineering, or mathematics had a higher OR for bone cancer than subjects whose fathers worked ≥5 years (OR = 1.5, 95% CI: 0.9-11.9). For all other occupations, the risk of bone cancer was not substantially different between the two categories of employment length.
The relative risk of bone cancer was high only after 2-5 years of sales (OR = 1.8, 95% CI: 0.2-18). Conversely, the OR was high for work in: medicine and health (OR = 2.0, 95% CI: 0.7-5.7); and farming, horticulture and animal husbandry (OR = 2.7, 95% CI: 0.7-11.7); and teaching (OR = 2.8, 95% CI: 1.3-6.3 and OR = 2.9, 95% CI: 0.5-15.3). No case mothers.

For all bone cancer types combined, elevated OR were observed for maternal employment in: farming, horticulture, and animal husbandry (OR = 2.7, 95% CI: 0.8-9.3); teaching (OR = 2.3, 95% CI: 1.2-4.6); managerial, administrative, and related (OR = 1.9, 95% CI: 0.7-5.3); product fabricating, assembling, and repairing (OR = 1.6, 95% CI: 0.6-4.5); and medicine and health (OR = 1.5, 95% CI: 0.8-3.7) (Table 2). Elevated OR were observed for osteosarcoma among subjects whose mothers had been employed in managerial and administrative occupations (OR = 2.3, 95% CI: 0.6-8.1); in product fabricating, assembling and repairing occupations (OR = 2.0, 95% CI: 0.6-7.2); teaching (OR = 1.8, 95% CI: 0.7-4.8); and medicine and health (OR = 1.8, 95% CI: 0.8-4.1). No case or control mothers.

With respect to Ewing's sarcoma, the relative risk was elevated for maternal employment in: farming, horticulture, and animal husbandry (OR = 7.8, 95% CI: 1.9-31.7); teaching (OR = 3.1, 95% CI: 1.1-8.7); managerial and administrative work (OR = 1.4, 95% CI: 0.2-10.9); and medicine and health (OR = 1.4, 95% CI: 0.5-4.1). In contrast, children of mothers ever employed in service occupations had an OR less than one (OR = 0.4, 95% CI: 0.1-3.1). No case fathers.

Results from dose-response analysis (Table 3) showed high OR for both categories of employment length (1-4 years, 5+ years) for three occupations: managerial and administrative (OR = 2.2, 95% CI: 0.7-7.3 and OR = 2.6, 95% CI: 0.3-26.1); teaching (OR = 2.8, 95% CI: 1.3-6.3 and OR = 2.9, 95% CI: 0.7-11.7); and farming, horticulture and animal husbandry (OR = 3.8, 95% CI: 0.6-23.3 and OR = 2.9, 95% CI: 0.5-15.3). The relative risk of bone cancer was high only after ≥5 years of work in: medicine and health (OR = 2.0, 95% CI: 0.7-5.7); and sales (OR = 1.8, 95% CI: 0.2-18). Conversely, the OR was high for maternal occupation in product fabricating, assembling and repairing when length of employment was 1-4 years (OR = 1.9, 95% CI: 0.6-6.3), but not after ≥5 years of employment (OR = 1.2, 95% CI: 0.1-10.7). The test for a dose-response relationship between length of employment and bone cancer was statistically significant only for maternal occupation in teaching (P < 0.05).

**Discussion**

This is one of the first large population-based studies to explore the relationship between parental occupation and childhood bone cancer. In light of the paucity of information on specific agents potentially contributing to the development of childhood bone malignancies, a hypothesis generating approach using occupational category was assumed. The findings from this study add to the accumulation of evidence regarding an association between parental occupation and childhood bone cancer. A number of studies, including the present report, have identified white collar parental occupations as being associated with increased risk, even though hazardous exposures are not expected to occur in these occupations.11-13 It is possible that these findings are influenced by socioeconomic status. Due to the lack of data on parental education and income, however, potential confounding by these variables was not examined. With respect to adult cancers, higher incidence and mortality from cancer of all sites combined among socioeconomically disadvantaged groups have been documented, with the greatest differences for cancers of the stomach, lung and cervix uteri.14 To date, findings of a positive association between parental socioeconomic status and childhood bone cancer have not been reported. A case-control study of childhood brain cancer found...
that case parents were more likely to have completed higher education and to hold white collar and professional jobs with no obvious carcinogenic exposure. It is possible that children from socioeconomically advantaged households experience a greater risk of developing bone cancer if they have a higher rate of growth, although to date this is still an unconfirmed risk factor for bone cancer in children.

The results of the present study also indicated an elevated risk associated with parental occupation in farming, horticulture, and animal husbandry. The lack of a dose-response relationship may be a consequence of the small number of subjects in each of the two exposed categories. Another possibility is misclassification among the three exposure categories. Unlike dichotomous exposure classification, multilevel exposure misclassification does not necessarily result in OR which are all biased toward one.

An association between parental occupation in agriculture and childhood cancer has been reported in other studies. With respect to childhood bone cancer specifically, there have been reports of a significantly increased risk of Ewing’s sarcoma among children whose fathers were employed in agricultural occupations. It is interesting to note, also, that two studies which examined childhood leukaemia and parental exposures reported increased risk among children of parents exposed to pesticides. In our study, 22 of 33 fathers who were ever employed in farming, horticulture, and animal husbandry provided information on workplace exposures. Five of seven cases, and 10 of 15 controls, reported exposure to fertilizers, pesticides, herbicides, insecticides, and/or fungicides. However, fathers also reported exposure to acids, explosives, gasoline, mineral dusts and fibres, and petroleum products.

Alternatively, the elevated bone cancer risk observed among offspring of parents in agricultural occupations may not have been mediated through the parents, but rather was the result of direct exposure experienced by the subjects themselves. In agricultural settings, it would not be unusual for children to experience many of the same exposures as their parents since many families who work on a farm reside there too. Findings from one study recorded the occurrence of six Ewing’s sarcoma cases within a 2-year period where all the cases resided in rural settings and reported exposure to farm animals, raising the possibility of an infectious aetiological agent which is transmitted by farm animals. To date, however, the development of bone cancer via transmission of an infectious agent has been demonstrated in animal experiments only.

The elevated OR associated with parental occupation in medicine and health are consistent with the results of previous studies associating medically-related occupations to childhood cancer. An increased risk of cancer among children of female pharmacists was reported in a Finnish study while a childhood leukemia study demonstrated significantly greater risk among children of fathers employed in medical and social services. Furthermore, Olsen et al. observed significantly increased risk of bone tumours for paternal, as well as maternal, employment in health care which comprised hospitals, physicians, dentists, maternity clinics, and physiotherapy clinics. Potentially hazardous exposures included the handling of drugs, sterilizing agents, anaesthetics, ionizing and non-ionizing radiation, and infections.

The results of our study should be considered in the context of various methodological limitations. One weakness is the use of job titles to infer occupational exposure. As exposures reported by fathers in the agricultural category show, a specific job title will usually encompass a group of workers with heterogeneous activities and exposures. Consequently, it is likely that only some of the workers were actually exposed to the causal agent. In this study, the nature of the misclassification was likely to be non-differential. Furthermore, because the questionnaire did not solicit information about leisure activities, potentially important recreational exposures were overlooked.

The lack of validation of occupation information is a limitation, since the majority of the questionnaires (including paternal occupation) were completed by the subject’s mother. Several studies evaluating the validity of paternal occupational history or paternal work exposure history as reported by the spouse have shown only fair concordance rates of approximately 59%. Moreover, most discrepancies were found to be the result of omissions by the wives. In our study, while missing information on paternal occupation and/or dates of employment reduced the dataset of eligible subjects, consequently decreasing the potential for the reported occupations to accurately reflect all occupations held by the subjects’ fathers, there is no reason to suspect that mothers of cases and controls differentially either omitted occupations or inaccurately reported dates of employment.

Because the frequency of Ewing’s sarcoma is known to be rare among Blacks and Orientals, the lack of information on ethnicity and the consequent lack of adjustment for this variable may have reduced the validity of the results, assuming that some occupations are occupied predominantly by specific ethnic groups. It is unlikely that these results are affected by ethnicity, however, since the Ontario population is relatively homogeneous, with non-whites comprising a comparatively small percentage of the population.

Since numerous statistical tests were performed during data analysis, the possibility of chance findings cannot be dismissed. One approach to address the issue of multiple testing is the Bonferroni adjustment of P-values. It has been argued that however, that this method is impractical, particularly for exploratory studies, since the adjusted significance level becomes overly stringent, making it virtually impossible to detect any risk. It can also be argued that statistical adjustment is unnecessary in this investigation since the occupations were evaluated separately and independently from one another. Consequently, the results from each occupation can be regarded as coming from a separate study.

While statistical testing provides an objective measure of evaluating the probability of an event, it is also important to acknowledge the magnitude and the precision of the odds ratio estimate, as well as evidence from other studies.

This investigation is the first large population-based study to examine paternal and maternal occupation in relation to childhood bone cancer. Unlike other studies, the large number of cases and controls permitted data analysis by histological type: previously, parental occupation in relation to osteosarcoma risk had not been explored. This is also the first study to examine the possibility of a dose-response relationship between length of employment and bone cancer risk among offspring, although there was a lack of significant findings.

While we do not purport to make causal inferences based on the findings of this study, the results taken in conjunction with findings from earlier investigations suggest that it would be worth pursuing research focusing specifically on agricultural
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References