

# Paternal Occupational Exposures and Childhood Cancer

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The objective of the study described here was to test the hypothesis that paternal occupational exposure near conception increases the risk of cancer in the offspring. We conducted a cohort study based on a population of 235,635 children born shortly after two different censuses in Sweden. The children were followed from birth to 14 years, and cases of cancer were identified in the Swedish Cancer Registry. Occupational hygienists assessed the probability of exposure to different agents in each combination of the father's industry and occupation as reported in the censuses. We also analyzed individual job titles. We compared the cancer incidence among children of exposed fathers to that among children of unexposed fathers using Cox proportional hazards modeling. The main findings were an increased risk of nervous system tumors related to paternal occupational exposure to pesticides [relative risk (RR) = 2.36; 95% confidence interval (CI), 1.27–4.39] and work as a painter (RR = 3.65; 95% CI, 1.71–7.80), and an increased risk of leukemia related to wood work by fathers (RR = 2.18; 95% CI, 1.26–3.78). We found no associations between childhood leukemia and paternal exposure to pesticides or paint. Our results support previous findings of an increased risk of childhood brain tumors and leukemia associated with certain paternal occupational exposures. Some findings in previous studies were not confirmed in this study. **Key words** brain tumors, cancer, children, leukemia, parental occupation, pesticides. *Environ Health Perspect* 109:193–196 (2001). [Online 29 January 2001] <http://ehpnet1.niehs.nih.gov/docs/2001/109p193-196feychting/abstract.html>

Despite extensive research, the etiology of childhood cancer is largely unknown. Considering the early onset of many childhood cancers—especially childhood acute lymphocytic leukemia, which is most common in children aged 2–5 years—risk factors occurring very early in life, during pregnancy, or even before conception must be considered. During the last decades, several studies have focused on parental occupational exposures that occurred prenatally as possible risk factors for various childhood cancers. So far, the only prenatal exposure established as a cause of cancer in the offspring is diethylstilbestrol, a drug that, when taken during pregnancy, can cause vaginal adenocarcinoma in daughters (1). Most studies of prenatal exposures have focused on paternal occupational exposures (2,3), and the strongest evidence has been found for childhood leukemia and paternal exposure to solvents, paints, pesticides, and employment in motor vehicle-related occupations, and for childhood nervous system tumors and paternal exposure to paints and pesticides. Most of the studies have been case-control studies.

The causal pathway for paternal exposures would be either that the father brings carcinogenic substances into the home where the child is exposed transplacentally through exposure of the mother, or that the exposure causes a genetic alteration in the father's sperm before conception that would affect cancer susceptibility in the child. Some evidence from experimental studies supports the hypothesis that exposure to exogenous agents before conception can alter the germ

cells, which may increase the risk of cancer in the offspring (4).

We conducted a cohort study to test the hypothesis that paternal occupational exposures before conception have an effect on the incidence of childhood cancer. Special attention was given to childhood leukemia and nervous system tumors, because these are the most common types of childhood cancer.

## Material and Methods

**Study base.** The study was designed as a cohort study based on a population of children born shortly after two different censuses in Sweden. All children born to married couples in 1976, 1977, 1981, and 1982 were included in the study. A child's mother can be identified easily in the population registry, but the father can be identified only if the couple were married at the time of the child's birth. Therefore, we restricted subjects to children born to married couples. The study base comprises 235,635 children. All children were followed from the day they were born until their 15th birthday, or to 1993, whichever came first. Thus, children born in 1976 and 1977 (54% of all children) were followed for 15 years, children born in 1981 (23%) for 13 years, and children born in 1982 (23%) for 12 years. We linked records to the Swedish Cause of Death Registry to identify the date of death for those children who had died before the end of the follow-up period. One percent of the children had died before the end of the follow-up period, and approximately 75% of those died within the first year of life. All cases of cancer were identified

through a record linkage to the nationwide Swedish Cancer Registry, operated by the National Board of Health and Welfare. We identified 522 cases of childhood cancer. Of these, 161 had leukemia [*International Classification of Diseases 8* (ICD 8): 204–207], 162 had nervous system tumors (ICD 7: 193), and 40 had lymphoma (ICD 7: 200–201). Results are reported only for leukemia and nervous system tumors, because the number of cases for other types of cancers was too small for meaningful analyses.

**Exposure assessment.** For children born in 1976 and 1977, we obtained information about the father's occupation from the census performed in 1975, and for children born in 1981 and 1982, we used information from the census performed in 1980. About 2% of the fathers were not found in the censuses. The information obtained from the censuses was the father's occupation and industry, and in the 1980 census socioeconomic status was also available. The censuses refer to the situation during 1 week in November of the census year. Therefore, the occupational information refers to a period 2–26 months before the child's birth. Five percent of the fathers were not working at the time of the census (3.1% were students). Of the fathers who were working, an occupational title was available for 98.7%. We linked fathers' occupational information with a job-exposure matrix (JEM) that was constructed specifically for this study. A JEM is a cross-tabulation of occupational information and exposure variables. In this JEM, occupational title and industry code were linked, and exposure was assessed for each combination of occupational title and industry. The occupations were classified according to the Nordic Occupational Classification [Systematisk förteckning över yrken 1975 (5)] at a three-digit level, which is a modification of the International Standard Classification of Occupations (ISCO). Industry was classified according to NGR 69 (Nordisk Näringsgrens Register 1969) (6), at a four-digit level, equivalent to *International Standard Industrial Classification* of all economic activities (ISIC), rev 2, 1968.

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Two senior occupational hygienists, each with 30 years of experience in industry, assessed the probability of exposure to different agents in each combination of industry and occupation. The classification was made according to a three-level scale: no exposure, possible exposure, and probable exposure. The exposures considered were asbestos, arsenic, pesticides, chromium/nickel, mercury, oil, general chemical exposures, solvents, metallic compounds, benzene, polyaromatic hydrocarbons (PAHs, combustion products), lead, and textile dust. The assessment of exposure was based on earlier experience of occupational exposure classification in epidemiological studies (7–10), and other JEM constructions (11), as well as extensive knowledge about the past and present working conditions at Swedish workplaces since the early 1970s.

The exposure in odd combinations of occupation and industry (links) was not assessed. The odd links usually contained very few subjects from a certain occupation. In these cases, the combination of occupation and industry is very unusual (e.g., dentist in the food industry). A link was considered odd if it contained less than 1% of the total number of subjects in the occupation; or in occupations with fewer than 500 subjects, a link was considered odd if it contained < 5% of the subjects in that occupation. As a result, approximately 15% of the subjects lacked information about the probability of these exposures in their father's occupation. The age distribution among mothers and fathers did not differ for children whose father's occupational exposure was not assessed compared to those with exposure assessment. Analyses were also made based solely on the father's occupational title.

**Statistical methods.** The relative risk of childhood cancer in relation to paternal occupation was estimated through Cox proportional hazards modeling using the SAS program PHREG (SAS Institute, Cary, NC, USA). Adjustments were made for census year, gender, and maternal age. Control of confounding from socioeconomic status was made in an analysis restricted to children born in 1981 and 1982.

## Results

Many of the investigated exposures were rare, and therefore the two exposure categories "possible exposure" and "probable exposure" were combined in most of the analyses. If the observed or expected number of cases was five or more, we also present the results for the category "probable exposure." The number of fathers exposed to arsenic or mercury was too low for any meaningful analyses, and no results are presented for

these exposures. Several other exposures were also rare, such as benzene exposure and lead exposure. Adjustment for maternal age and socioeconomic status in the analyses did not change any of the results, so results presented here are adjusted only for census year and gender. Table 1 presents the results for childhood leukemia and nervous system tumors. An indication of an increased risk of childhood leukemia is seen among children whose fathers were exposed to textile dust. A modestly increased risk was found for paternal solvent exposure. Although, as already mentioned, benzene exposure was too rare for a meaningful analysis, the leukemia risk in children younger than 5 years was 2.0 (95% CI, 0.6–6.3), based on three exposed cases. The results for childhood nervous system tumors showed an increased risk related to paternal exposure to pesticides. The risk of nervous system tumors was increased among children whose fathers worked in occupations classified as having probable exposure to solvents: 2.48 (95% CI, 1.29–4.76), based on 10 exposed cases.

Tables 2 and 3 present the results for paternal job titles related to childhood leukemia and nervous system tumors, respectively. A two-digit classification of the occupation was used. Only occupational categories with five or more observed or expected cases are presented, unless there was a statistically significant association between the occupation and the outcome. For occupations where an association with the outcome is indicated, results are shown also for subdivisions of the occupation into finer categories using a three-digit classification. An increased risk of childhood leukemia was found for children whose fathers had an occupation involving government legislative and administrative work. This occupational category could not be subdivided into finer categories. Increased risks were also found for "other" saleswork, such as commercial travelers, shop managers, shop assistants, and filling station attendants. Within the occupational category "engineering and building metal work," fathers' occupation as sheet metal worker was associated with a 4-fold risk of childhood leukemia.

Wood work was associated with a doubled risk for childhood leukemia. For childhood nervous system tumors, an increased risk was found for children whose fathers worked with engineering, largely based on an elevated risk for mechanical engineers and technicians. Agricultural work was also associated with an increased risk for nervous system tumors in the offspring. Having a father who worked as a painter was associated with more than a 3-fold increased risk. An elevated risk estimate was found for children whose fathers worked as firefighters, but this result is based on a very small number of exposed cases.

## Discussion

The main findings of this study were an increased risk of nervous system tumors related to paternal occupational exposure to pesticides, solvents, and work as a painter, and an increased risk of leukemia related to paternal occupational exposure to textile dust, wood work, and sales work.

The strength of this study is that it is a population-based cohort study where all information about the exposure has been collected before the occurrence of cancer. Thus, recall bias is of no concern. Furthermore, the Swedish Population Registry was used to identify children and their parents, which means that selection bias is unlikely to affect the findings. The Swedish Cancer Registry used to identify cases of cancer covers the entire nation, and reporting of new cases of cancer is compulsory. Reports are sent to the Cancer Registry both from the treating physician and from the pathologist or cytologist. Thus, the registry covers approximately 96% of all cases (12).

The major weakness of this study is the exposure assessment. The exposure was classified based on the occupational title and industry as reported in the census performed 2–26 months before the child's birth. The annual turnover frequency was about 10% among low-skilled workers where most exposures occurred, and their exposure pattern may have changed since their occupation classification. The level of exposure may vary within an occupational title, and taking

**Table 1.** Father's occupational exposure before conception (possible and probable exposure combined).

	Leukemia		Nervous system tumors	
	No. cases	RR (95% CI)	No. cases	RR (95% CI)
Asbestos	10	0.97 (0.51–1.85)	6	0.64 (0.28–1.46)
Pesticides	5	0.90 (0.37–2.19)	11	2.36 (1.27–4.39)
Chromium/nickel	5	1.18 (0.48–2.88)	1	0.26 (0.04–1.85)
Oil	11	0.93 (0.50–1.72)	10	0.96 (0.50–1.83)
General chemical exposure	6	0.57 (0.25–1.29)	10	1.12 (0.59–2.14)
Solvents	23	1.25 (0.80–1.95)	19	1.15 (0.70–1.87)
Metallic compounds	5	0.98 (0.40–2.40)	1	0.22 (0.03–1.54)
Benzene	3	1.23 (0.39–3.85)	2	0.91 (0.23–3.70)
PAHs (combustion products)	11	0.84 (0.45–1.55)	11	0.96 (0.52–1.78)
Lead	1	1.04 (0.15–7.34)	2	2.37 (0.59–9.58)
Textile dust	8	1.67 (0.82–3.40)	3	0.68 (0.22–2.14)

industry into consideration only partially accounts for this variation. This type of exposure misclassification is unlikely to be related to the disease and cannot explain the observed increased risk estimates. However, such misclassification may hamper the ability to detect an association should one exist. Furthermore, the exposure classification did not allow evaluation of dose-response patterns.

Several of the exposures were rare in our data, leading to unstable risk estimates. This made it impossible to evaluate the effect of paternal occupational exposure to benzene or lead, for example. Furthermore, the small number of exposed cases did not allow for analyses of specific subtypes of leukemia or nervous system tumors, which is a limitation because these subtypes may have different etiologies.

The focus of this study was on paternal occupational exposure immediately before conception of the child. Because we had information about occupation only from one point in time, we could not separate the exposure before conception from exposure occurring during pregnancy or after the child was born. Thus, the increased risk of nervous system tumors observed in children whose fathers were occupationally exposed to pesticides before conception may be explained by exposure of the child after birth. Most of the pesticide exposure came from agricultural work, which means that the child may have lived on a farm and received direct exposure. The other exposures for which an association was found in this study are to substances that the father would have to bring into the house for the child to receive exposure after birth.

Only limited control of confounding could be made. However, there are few known risk factors for childhood cancer, and to be a confounder the risk factor must be related both to the risk of childhood cancer and to paternal occupational exposures. Those confounders that were controlled in the analysis did not affect the results (socioeconomic status, maternal age, gender, time period). However, we cannot rule out the possibility that confounding from some unknown risk factor could explain our findings.

In our data, most occupations involving pesticide exposure were agricultural, horticultural, forestry, or livestock work. Several previous studies also have reported increased risk of brain tumor in the offspring related to paternal agricultural work or residence on a farm [reviewed by Daniels et al. 1996 (13), and by Zahm and Ward 1998 (14)]. Most of the studies have focused on the period before conception or during pregnancy. Several studies found a stronger effect for exposures before conception than during

pregnancy or childhood (15,16), although one study found the highest risk associated with farm residence during childhood (17). The only previous cohort study found an increased risk of brain tumor in the children

of farm owners and a dose-response relationship where amount of pesticide exposure was estimated through information about money spent on pesticides (18). For childhood leukemia, Kristensen et al. (18) found

**Table 2.** Leukemia risk related to paternal occupation before conception.

ISCO code	Occupation	No. cases	RR (95% CI)
0	Engineering work	15	0.78 (0.46–1.33)
5	Educational work	9	1.18 (0.60–2.32)
9	Other professional, technical, and related work	4	0.63 (0.24–1.71)
10	Government legislative and administrative work	5	2.72 (1.12–6.64)
29	Clerical and related work	5	0.82 (0.34–2.00)
33	Other sales work	17	1.79 (1.08–2.96)
331	Commercial travelers, buyers, dealers	10	1.52 (0.80–2.88)
332	Shop managers	2	2.23 (0.55–9.01)
333	Shop assistants	4	2.02 (0.75–5.44)
338	Filling station attendants, demonstrators	1	2.89 (0.40–20.57)
40	Agricultural, horticultural, and forestry management	5	1.12 (0.46–2.74)
63	Railway engine drivers and assistants	6	0.79 (0.35–1.78)
75	Engineering and building metal work	23	1.26 (0.81–1.96)
750	Toolmakers, machine-tool setters, and operators	7	1.40 (0.66–2.99)
751	Machinery fitters, machine assemblers	3	0.37 (0.12–1.17)
753	Sheet metal workers	7	4.10 (1.92–8.75)
754	Plumbers and pipe fitters	1	0.72 (0.10–5.16)
755	Welders and flame cutters	4	1.51 (0.56–4.08)
757	Metal platers and coaters	1	7.19 (1.01–51.40)
76	Electrical and electronics work	9	1.32 (0.67–2.59)
77	Wood work	14	2.18 (1.26–3.78)
771	Construction carpenters and joiners	9	2.29 (1.17–4.49)
772	Bench carpenters and cabinet makers	5	2.90 (1.19–7.08)

**Table 3.** Nervous system tumor risk related to paternal occupation before conception.

ISCO code	Occupation	No. cases	RR (95% CI)
0	Engineering work	26	1.49 (0.98–2.27)
001	Architects, building and construction engineers, and technicians	4	0.85 (0.32–2.30)
002	Electrical, electronics, and telecommunications engineers and technicians	5	1.21 (0.49–2.94)
003	Mechanical engineers and technicians	11	1.93 (1.04–3.57)
004	Chemical engineers and technicians	2	1.72 (0.43–6.93)
5	Educational work	5	0.65 (0.27–1.58)
8	Literary and artistic work	5	2.81 (1.15–6.86)
9	Other professional, technical, and related work	2	0.32 (0.08–1.29)
11	Business administrative and other technical and economic administrative work	5	1.86 (0.76–4.54)
111	General managers	3	3.78 (1.21–11.87)
118	Other business managers	2	1.04 (0.26–4.20)
29	Clerical and related work	7	1.18 (0.55–2.51)
33	Other sales work	4	0.39 (0.14–1.05)
331	Commercial travelers, buyers, dealers	3	0.44 (0.14–1.38)
332	Shop managers	0	
333	Shop assistants	1	0.50 (0.07–3.57)
338	Filling station attendants, demonstrators	0	
40	Agricultural, horticultural, and forestry management	9	2.12 (1.08–4.16)
401	Working proprietors (agricultural, horticultural, and forestry)	6	1.63 (0.72–3.70)
403	Forestry managers and supervisors	2	7.17 (1.78–28.92)
404	Horticultural managers and supervisors	1	7.18 (1.01–51.30)
41	Agricultural, horticultural, and livestock work	3	1.84 (0.59–5.77)
411	Agricultural and livestock workers	3	2.97 (0.95–9.32)
63	Railway engine drivers and assistants	7	0.94 (0.44–2.00)
66	Mail distribution and other messenger work	4	2.88 (1.07–7.77)
661	Sorting clerks and postment	1	1.01 (0.14–7.19)
662	Messengers	3	7.27 (2.32–22.82)
76	Electrical and electronics work	7	1.02 (0.48–2.19)
77	Wood work	5	0.74 (0.30–1.80)
78	Painting work	7	3.65 (1.71–7.80)
90	Civilian protective service work	6	1.93 (0.85–4.36)
901	Firefighters	3	5.89 (1.88–18.47)
902	Policemen	2	1.27 (0.31–5.12)

risk estimates close to unity. Overall, the results for childhood leukemia in relation to paternal agricultural occupations are more inconsistent. Lowengart et al. (19) found no association with paternal occupation in agriculture, but significantly increased risk estimates for childhood leukemia in relation to both paternal and maternal pesticide use in the home and in the garden. Several other studies have observed risk estimates close to unity in relation to paternal agricultural occupations (20–23), while others have observed increased risks (24–26). A recent study found increased risks for acute lymphoblastic leukemia in children related to paternal occupational exposures to pesticides and fertilizers before conception (27). Pesticide practices may differ between countries. In Sweden pesticide use has been strictly regulated by authorities, and the exposure time per year is very short. Farmers are also exposed to diesel exhaust, solvents, and motor vehicle exhaust.

An increased risk of nervous system tumors (or brain tumors) related to paternal occupational exposure to paint has been observed in several previous studies (20,28), but Johnson et al. (29) found no increased risk. Several studies have also linked leukemia in the offspring to paternal exposure to paint (19,20,30), which was not confirmed in this study.

The increased risk of brain tumors related to paternal occupational exposure to solvents in this study depends to some extent on the increased risk among children of painters. However, if painters are excluded, a slightly increased risk still remains, although based on a small number of cases. Several studies have reported an increased risk of childhood leukemia related to paternal exposure to solvents (19,30,31). In this study we found only a modestly increased risk. We found, however, an increased risk of leukemia related to paternal work as a carpenter, which may involve exposure to solvents. Wood work by fathers has been associated with leukemia in their children in some previous studies (25,31). Olsen et al. (32) found no association with childhood leukemia, but an increase in the risk of childhood brain tumors.

Most studies of parental textile work have focused on maternal exposure. However, a couple of studies have also linked paternal textile work to childhood leukemia (19,25). In the present study an increased risk was indicated, although based on a small number of subjects. Textile exposure occurred for tailors, textile workers, and clothing salesmen.

The underlying hypothesis in studies of paternal preconceptional exposures is that some environmental factors can act on the germ cells of the father before conception

and cause DNA alterations, which can affect cancer susceptibility in their children. Experimental studies have shown that parental exposure to chemicals before mating can increase cancer incidence in mice and rats in following generations (4). There is some evidence from epidemiological studies of a transgenerational effect on cancer incidence in humans, although the evidence cannot be viewed as conclusive. The results in this study support several of the findings of previous studies.

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