Occupations of fathers of patients with Wilms's tumour

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SUMMARY A case-control study of 149 Connecticut-born children with Wilms's tumour reported to the Connecticut Tumor Registry during the period 1935–1973 and of 149 matched controls was undertaken in order to explore the possibility that children with Wilms's tumour may have been exposed perinatally to carcinogenic agents. The occupation of the father at the time of the child's birth was investigated and used as an indicator of potential sources of carcinogens to which infants in the study may have been exposed. An association was found between paternal occupations related to lead in the group developing Wilms's tumour compared with the controls.

The fact that most cases of Wilms's tumour, a childhood neoplasm of the kidney, are diagnosed before the age of four suggests that factors operating at the time of conception, during pregnancy, or soon after birth may be important in the aetiology of this neoplasm. A genetic predisposition to the disease has been reported, as well as an association with several congenital malformations, particularly aniridia and hemihypertrophy (Miller *et al.*, 1964; Knudson and Strong, 1972; Pendergrass, 1976).

Little information is available on specific environmental factors that may influence the occurrence of Wilms's tumour. Fabia and Thuy (1974) studied the occupations of fathers at the time of birth of children who died of neoplasms. They found an excess of hydrocarbon-related occupations in fathers of children who developed cancer but not among the fathers of the few patients in their series with Wilms's tumour. In a subsequent study, Hakulinen *et al.* (1976) found no relation between father's occupation and childhood cancer; cases of Wilms's tumour were not analysed separately.

The hypothesis that perinatal exposure to carcinogens may be associated with the subsequent occurrence of Wilms's tumour was tested in this study of children who entered the Connecticut Tumor Registry during a 38-year period.

Material and methods

All 149 patients with a diagnosis of Wilms's tumour, who were born in Connecticut and reported to the Connecticut Tumor Registry during the 1935–1973 period, were entered in this study (80 males and 69 females). Cases ranged in age from the newborn to 19 years; 133 were white and 16 were black. Bilateral involvement was reported in two patients. The 149 controls were selected from the Connecticut State Health Department files of birth certificates and matched with the cases for sex, race, and year of birth. No cancers were found among the controls. Information on cases and controls, obtained exclusively from birth certificates, included the occupation of the father. The classification of occupations was similar to that employed by Fabia and Thuy (1974) and Hakulinen *et al.* (1976). Table 1 lists the 22 broad groups of occupations which were used in this study. Among them, six occupations are known to have considerable exposure to hydrocarbons and seven to lead, a major additive to petrol, also present in car exhaust fumes. The occupations—dyer, miner, lumberman, and painter—included as hydrocarbon-related by Fabia and Thuy (1974) and Hakulinen *et al.* (1976) were not represented in our study.

Table 1 *Distribution of children with Wilms's tumour and controls according to occupation of father at time of birth*

Occupation	Cases	Controls
1. Professional, administrator	26	26
2. White collar worker	22	25
3. Farmer	1	8
4. Machinist*	5	3
5. Cleaner*	2	1
6. Embalmer*	0	1
7. Driver*†	8	4
8. Motor vehicle mechanic*†	6	1
9. Service station attendant*†	3	0
10. Welder†	3	0
11. Solderer†	1	0
12. Metallurgist†	1	0
13. Scrap metal worker†	0	1
14. Factory worker, not elsewhere classified	32	33
15. Construction worker	1	2
16. Electrician, plumber, carpenter	7	10
17. Tailor, weaver, furrier, shoemaker	4	3
18. Butcher, dairy worker, cook	2	2
19. Other miscellaneous blue collar	10	10
20. Unknown	9	9
21. Unemployed, student	0	4
22. Armed Forces	6	6
TOTAL	149	149

* Hydrocarbon-related occupation.

† Lead-related occupation.

In order to assess the comparability of cases and controls, other maternal and paternal factors entered on the birth certificates (mother's pregnancy history, parent's age and place of birth, child's birthweight, and length of gestation) were examined and found to be similar in these two groups. MacMahon and Newill (1962) also reported that birth characteristics of children dying of malignant neoplasms did not differ from those of controls.

In the case-control comparison of birth certificate variables, the χ^2 test for paired observations and the Student's *t* statistic for paired samples were used. The McNemar test on a dichotomous outcome from matched pairs, incorporating Fisher's exact probability, was used instead of the χ^2 test if one of the off-diagonal frequencies in the resulting 2×2

table was less than five. Estimates of odds ratios and their confidence intervals were calculated according to the method for individually matched series as described by Miettinen (1970).

Results

The distribution of children with Wilms's tumour and matched controls according to their fathers' occupations at the time of birth is shown in Table 1. The distribution of both groups was similar for offspring of professionals and administrators, and of white collar workers, suggesting that cases and controls were comparably distributed by social class (Hollingshead, 1957).

Both cases and controls had similar distribution of urban and rural births: thus the larger number of farmers among fathers of controls cannot be explained.

Fathers of 24 Wilms's tumour patients and 10 controls were in occupations considered to be hydrocarbon-related, yielding an odds ratio of 2.4 ($\chi^2 = 4.97$; $P = 0.026$; 95% confidence interval 1.1 to 5.7).

The excess among the case group of fathers employed in hydrocarbon-related occupations was contributed largely by occupations with exposure to petrol and its combustion products, that is, driver, motor vehicle mechanic, and service station attendant, where exposure to lead is known to occur.

Fathers of 22 Wilms's tumour cases and of six controls were found to be in lead-related occupations (driver, motor vehicle mechanic, service station attendant, welder, solderer, metallurgist, and scrap metal worker) as seen in Table 1. The resulting odds ratio is 3.7 ($\chi^2 = 8.04$; $P = 0.005$; 95% confidence interval 1.5 to 11.1).

Odds ratios calculated in Table 2 show that exposure to lead yields the highest risk of Wilms's tumour.

Thirteen fathers of cases and five fathers of controls who were in lead-related occupations were parents of older children born in Connecticut.

Table 2 *Odds ratios for hydrocarbon- and lead-related occupations*

Occupational exposure	Number of fathers		Odds ratio
	Cases	Controls	
Lead exposure only	5	1	5.00 (5.75)*
Hydrocarbon exposure only	7	5	1.40 (1.61)
Both lead and hydrocarbon exposure	17	5	3.40 (3.91)
Neither exposure	120	138	0.87 (1.00)

* Number in parentheses represent odds ratio for this exposure divided by odds ratio for neither exposure.

Information from the birth certificates of these earlier offspring indicated that 11 (85%) and two (40%) respectively reported the same lead-related occupation at the time of birth of the elder siblings (the average time between births of these two offspring was 4.5 years in the case group and 2.3 years in the control).

There were no reports of multiple primaries (other than bilateral involvement) among Wilms's tumour patients in the Connecticut Tumor Registry. Cancers in siblings occurred in the families of five cases, none in families of controls. Two siblings developed Wilms's tumour. All other cancers in siblings were diagnosed after the birth of the Wilms's tumour index case. None of the five fathers of siblings with cancer were employed in hydrocarbon- or lead-related occupations. Cancer occurred in the offspring of one male and one female patient with Wilms's tumour: the fathers of these two index cases were not employed in hydrocarbon- or lead-related occupations. The father of one of the two children with bilateral Wilms's tumour was employed in a hydrocarbon-lead-related occupation.

Discussion

In this study a significantly greater number of fathers of children with Wilms's tumour were in lead-related occupations as compared with controls (odds ratio = 3.7). As was mentioned earlier, only hydrocarbon-related occupations have been reported more frequently among fathers of children with cancer than controls, but not among fathers of children with Wilms's tumour.

In the United States of America, the average 'normal' blood-lead levels have ranged from 0.014 mg/100 ml in rural areas to 0.022 mg/100 ml in urban areas (Hofreuter *et al.*, 1961). Welders, solderers, metallurgists and scrap metal workers are likely to have mean blood-lead levels of 0.040 mg/100 ml or above. They are at a high risk of lead poisoning (that is, blood-lead exceeding 0.08 mg/100 ml) (Raymond *et al.*, 1960; Bustelo, 1962; Benevenuti, 1972). The mean blood-lead level in garage mechanics has been found in several studies to be about 0.035 mg/100 ml (Hofreuter *et al.*, 1961; Tola *et al.*, 1972); this finding may be explained in part by the fact that many greases contain lead naphthenate which can be absorbed through the skin (Hine *et al.*, 1969). Service station attendants have been reported to have mean blood-lead levels higher than 0.030 mg/100 ml (Kehoe *et al.*, 1969; Moore *et al.*, 1976). Motor vehicle drivers have been found to have on the average blood-lead levels 10%–15% lower than service station attendants but 30% higher levels than other urban residents (Haag, 1975).

Lead appears to have the capacity to cause chromosomal changes after short exposures to relatively small doses, and at blood-lead levels long considered compatible with normal physiological function. Cultured lymphocytes of workers whose blood-lead levels rose from 0.034 to 0.045 mg Pb/100 ml after a month of increased lead exposure have shown doubling of the percentage of abnormal metaphases (Forni *et al.*, 1976). These increased numbers of chromosomal abnormalities persisted for several months when blood-lead remained above 0.040 mg/100 ml. Some reversal of these changes was observed after a few weeks away from lead exposure. Teratospermia has been observed to range from 16% to 86% among men with occupational exposures to lead, in linear association with blood-lead levels ranging from 0.023 to 0.075 mg/100 ml (Lancranjan *et al.*, 1975).

The two-step mutation process, proposed by Knudson and Strong (1972) to explain Wilms's tumour, states that the first mutation may be a germinal (prezygotic) or a somatic event. It seems reasonable to assume that an effect of lead on spermatogenesis at the time of conception may be a prezygotic event that could play a role in the aetiology of Wilms's tumour.

Since it has been established that Wilms's tumour can be associated with a familial factor and with the presence of congenital anomalies, it would be useful to determine whether other renal parenchymal abnormalities associated with Wilms's tumour are found in patients whose fathers have been exposed to lead (Bove and Adams, 1976).

The percentage of patients with Wilms's tumour in this study whose fathers had been exposed to lead (15%) is relatively low, and may suggest that this cause is only a possible explanation of a small proportion of cases.

In this study, tests for lead intoxication were not performed on children with Wilms's tumour, their parents, or the controls. In the future, such tests may provide additional evidence implicating lead as an aetiological factor in Wilms's tumour.

We thank Dr. R. Monson, Harvard School of Public Health; Dr. J. Fraumeni, Jr., National Cancer Institute; Dr. E. Curnen, Jr., College of Physicians and Surgeons of Columbia University; Dr. H. Kantor, George Washington University Medical Center; Mrs. L. Turgeon, Columbia University School of Public Health; Mr. H. Burdo, Public Health Statistics Section of the Connecticut State Department of Health; the staff of the Connecticut Cancer Epidemiology Unit; Ms. A. Stark; Ms. J. Hooper; and Ms. C. Palmieri.

This study was supported by Public Health Service Contracts NO1 CP 33235 and NO1 CP 43203 from the National Cancer Institute.

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