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PARENTAL OCCUPATION AND INTRACRANIAL NEOPLASMS OF CHILDHOOD: RESULTS OF A CASE-CONTROL INTERVIEW STUDY

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In 1983-1984, the authors conducted a case-control study of environmental factors and childhood brain tumor risk. Cases (n = 110) were identified through the tumor registry of a pediatric hospital and matched controls (n = 193) through random digit dialing. In addition to parental occupational histories, telephone interviews elicited information about potential confounders and hypothesized risk factors for childhood brain tumors. Relying primarily on the Hoar et al. (*J Occup Med* 1980;22:722-6) job-exposure matrix, the authors examined parental employment characteristics in relation to the relevant developmental periods. Paternal employment in several industries (agriculture, construction, metal, and food and tobacco) and in several occupations (agriculture, benchwork, and transportation) was associated with excess risk. The range of notably elevated odds ratios was 2.0-3.3, with all confidence intervals including 1.0 except one. Elevated but unstable odds ratios were also found for both paternal and maternal employment in jobs "clustered" together because of common exposures. For both approaches to exposure classification, the greatest excess risks were consistently demonstrated for parental jobs held in the preconception period. Job-exposure matrix analyses indicated that case fathers were more likely than control fathers to have had jobs linked with aromatic amino and aromatic nitro compounds (range of notably elevated (and unstable) odds ratios, 3.4-4.4), but here the greatest excess risks were exhibited in the postnatal period. Few associations emerged for maternal employment characteristics, although this is probably explained by the relatively small number of women employed in jobs outside the home.

brain neoplasms; carcinogens, environmental; child; environmental exposure; occupational medicine

Epidemiologic studies of parental occupation and childhood cancer date back to 1974, when Fabia and Thuy (1) reported a twofold excess risk of cancer death among children less than 5 years of age whose fathers had jobs classified as "hydrocarbon-related." Since then, the relevant literature has grown considerably (2-37).

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Abbreviations: CI, confidence interval; OR, odds ratio.

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A small subset of these studies focused on childhood brain tumors (6, 9, 15, 18, 19, 27, 33, 35, 37). The results of these studies taken as a whole are not consistent (36), although statistically significant associations have been reported for parental jobs involving exposure to solvents (6), paints (6, 7), metals (33), and ionizing (24, 35) and nonionizing (37) radiation. Significantly elevated odds ratios have also been reported for jobs classified as hydrocarbon-related (9, 19) and for employment in the following industries: food and tobacco (27); aerospace (6); newspaper and printing (19); agriculture (27, 33); transportation (27, 33); construction (33); machinery (33); rubber, plastics, and synthetics (27); medicine and science (27); and metal (33). Implicated paternal occupations include metal-related occupations (33), printing work (19), graphic arts work (19), chemical and petroleum refinery work (19), chemical and drug sales (19), structural work (33), and electrical (or electronic) assembling, installing, repairing, or manufacturing (33, 37).

The results presented here derive from a case-control interview study of environmental factors and childhood brain tumor risk conducted in the central Ohio area. With respect to the parental occupation/childhood brain tumor hypothesis, it was our purpose, first, to attempt a replication of earlier findings by comparing case and control parents in terms of broad categories of industry and occupation. Second, attempts were made to refine this approach by using the job cluster methodology of Hsieh et al. (38). We also present here the results of using the job-exposure matrix of Hoar et al. (39) to test the a priori hypothesis that case parents were more likely than control parents to have had jobs before, during, or after the index pregnancy that involved exposure to *N*-nitroso compounds—a family of chemicals that includes several potent neurocarcinogens (40, 41). Empirical evidence reported by Preston-Martin et al. (42) is consistent with the view that in utero exposure to *N*-nitroso compounds may increase the risk of childhood central nervous system tumors.

As noted above, we have considered the relation of parental occupation to childhood brain tumor risk relative to the developmental periods of interest. If workplace exposures of parents are causally related to central nervous system tumors in the offspring, then different biologic mechanisms could be hypothesized: damage to parental germ cells, transplacental carcinogenesis, and postnatal exposure of children from contaminated fomites brought into the home.

Materials and Methods

Case ascertainment

In identifying cases through the Columbus, Ohio, Children's Hospital Tumor Registry, registry files for the 8-year period January 1, 1975, through December 31, 1982, were examined. Records were abstracted for each patient less than 20 years of age having a stated diagnosis of primary malignant neoplasm of the brain (*International Classification of Diseases, Eighth and Ninth Revisions,* code 191 (malignant neoplasm of the brain and central nervous system)). In addition to the patient's name, address, telephone number, and date of birth, the following information was obtained: age at diagnosis, date and place of diagnosis, vital status at last follow-up, histologic type and anatomic site of tumor, and name and address of the patient's physician. Patients whose tumors were judged inoperable and were not microscopically confirmed were also included in the study.

The physician of each patient satisfying study inclusion criteria was contacted to obtain permission to seek the parents' participation in the study and to update information regarding the patient's vital status.

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If permission to contact a family was denied, the subject was excluded.

Identification of controls

Attempts were made to select by random digit dialing two living, cancer-free, population-based controls, individually matched to each case by year of birth, race, and sex. To accomplish this, we estimated the subset of Ohio counties corresponding to the Columbus Children's Hospital referral area and constructed a sampling frame from the associated three-digit telephone exchanges. Specification of the appropriate subset of Ohio counties was accomplished in a manner similar to that previously described: The county of residence of each case at the time of diagnosis was mapped, with attention focused on the areal pattern in relation to the Ohio counties having a pediatric hospital (11, 12). Any county presumed to be in the Columbus Children's Hospital referral area but bordering a county having a pediatric hospital or other tertiary care facility known to admit children with serious illnesses was excluded. Counties on the periphery of the referral area but not bordering a county having such a facility were included or excluded on the basis of the expected number of cases for the study period (11, 12, 43). Medical care referral patterns of pediatric populations in Ohio were also considered in specifying the referral area, which was determined to be 48 contiguous counties. To avoid the potential overmatching on parental occupation that might result from matching on any close geographic or residential basis, we did not use the three-digit telephone exchange as a matching factor.

To select controls, we first obtained all three-digit telephone exchanges corresponding to the referral area along with the number of working residential telephone lines per exchange. Next, a three-digit exchange was selected from among the eligible three-digit exchanges. The probability of exchange selection was weighted by the number of working residential telephone lines per exchange, since this varied widely among exchanges. Once the three-digit exchange had been selected, a randomly selected four-digit number was attached, completing the number. If the number was determined to be nonworking or nonresidential before the first call was made, a new four-digit number was chosen and was attached to the same exchange. The working residential number was called a maximum of seven times, once per day for a period of 1 week, at various times of the day. If a call could not be completed or if it was determined to be nonworking or nonresidential after calling began, a new exchange was selected. When a call was completed, the eligibility of household members was determined through a series of screening questions and a call-back time arranged when appropriate.

The interview

Attempts were made to interview separately the biologic parents of all subjects. Most questions were designed for the biologic mother, except for questions pertaining to the father's occupation and demographics. If one of the biologic parents was deceased, his/her whereabouts were unknown, or he/she was unwilling to participate, a knowledgeable surrogate was used. Eligible surrogates included the spouse or a close relative of the unavailable parent.

The interview was designed specifically for this study and was conducted over the telephone. All interviewers were carefully trained, since interviewer blinding as to case-control status was not performed. Respondents were questioned on the following: parental demographics; residential histories; parental occupational histories (coded according to both the *Dictionary of Occupational Titles* (44) and the *Standard Industrial Classification Manual* (45)); use of selected household products, including pesticides; hobbies and pets; index pregnancy and birth characteristics; maternal diet during pregnancy; other pregnancies; active and passive exposure to tobacco

smoke; maternal illnesses and relevant medical conditions; maternal immunization history; maternal use of medications during pregnancy; maternal radiation exposure; and various child characteristics, including radiation exposure. Data collection focused on three specific time periods: the postnatal period (birth to diagnosis), the prenatal period (stratified by trimester when appropriate), and the preconception period (defined as the 12-month period prior to the estimated month of conception). Depending on the number of residential and occupational histories reported, most maternal interviews required 90–120 minutes for completion. Interviews of fathers lasted, on average, 15 minutes.

Exposure classification methods

Evaluation of the hypothesized association between parental occupation and childhood brain tumor risk relied primarily on the job-exposure matrix described by Hoar et al. (39) and on the job clustering scheme derived from the Hoar et al. data by Hsieh et al. (38). Analyses were conducted separately for the postnatal, prenatal, and preconception periods and focused during the prenatal and preconception periods on the "primary" job of the parent (i.e., on the job held the longest). Multiple jobs in the typically longer postnatal period were treated by the method of Flanders and Rothman (46), i.e., subjects were assigned to the reference category if and only if the primary *and* secondary jobs were considered low exposure.

In the first stage of analysis, parents were classified with respect to their *industry* of employment by the method of Hoar et al. (39). This classification scheme derives from the *Standard Industrial Classification Manual* (45) and inherently contains a grouping of "low-exposure" industries, which was used as the reference group in estimating industry-specific odds ratios. Parents were also classified with respect to their industry-specific *task* by the scheme described in the *Dictionary of Occupational Titles* (44). For odds ratio estimation here, a reference group was created by combining low-exposure occupations in the manner of Wilkins and Koutras (33).

In addition to basing case-control comparisons on broad categories of parental industry and occupation, we classified jobs for the second stage of analysis by the job cluster methodology of Hsieh et al. (38). Clusters derived from the Hoar et al. data represent groupings of jobs similar to one another in the estimated degree of exposure to each of the 24 agent groups in the job-exposure matrix of Hoar et al. For each cluster, Hsieh et al. defined agent-specific degree-of-exposure designators as follows: 0 = no exposure potential, 1 = light exposure, 2 = moderate exposure, 3 = heavy exposure, and 9 = exposure of unknown degree. Because several clusters contained small numbers of subjects, their dendogram (38, p. 582) was used to construct six new ones (0 + 1, 4 + 5, 6 + 7, 10 + 11 + 12, 16 + 17, and 22 + 23 + 24), reducing the overall number of clusters from 30 to 22. Here, cluster 0 + 1 was treated as the low-exposure reference group, since 22 of the 24 degree-of-exposure designators in this combined category were less than or equal to 0.5.

For the last phase of analysis, we selected a priori any nitrosamine or nitrosamide, any nitrosatable amino compound, and any compound having a chemical structure similar to that of the *N*-nitroso group from among all possible organic chemicals in the Hoar et al. (39) system. Consequently, all amines, amides, and ureas in the system were selected, as were all aromatic amino and aromatic nitro compounds. In total, 35 compounds were studied, with case and control parents classified as exposed if and only if the degree-of-exposure designator was greater than or equal to 2.0 (i.e., moderate-to-heavy exposure) or 9.0 (exposure present but degree unknown). The reference group here consisted of parents whose jobs were classified as cluster 0 + 1.

Statistical analysis

To preserve the *n*-to-1 matching of the study design, we calculated odds ratios and their 95 percent confidence intervals by the conditional logistic regression procedure described by Harrell (47). Odds ratios were not computed if any industry grouping, occupational grouping, or job cluster had fewer than 10 subjects.

RESULTS

Description of the case series

Tumor registry records of 151 young patients (99 males and 52 females) were found to meet study inclusion criteria. Selected characteristics of the total case series and of the subset with completed interviews are summarized in table 1. Almost all cases were white, and nearly two thirds were male. Most cases (64.9 percent) were less than 10 years of age at diagnosis, with the median age at diagnosis being 7.3 years. The distribution of histologic types of pediatric brain tumors was not atypical for a hospital-based series (48), although the number of medulloblastoma diagnoses was slightly higher than might have been expected. The size of the case group precluded meaningful subgroup analyses, i.e., analyses by clinical characteristics such as histologic type, anatomic site, or age at diagnosis. Only relatively minor differences were seen between the total case series and the subset with completed interviews (table 1).

Among the 151 eligible cases, the families of 14 could not be traced and the physicians of seven withheld permission for contact. Of the remaining 130 eligible cases, 110 interviews (72.8 percent of all eligible cases) were successfully completed during the period April 1, 1983–June 1, 1984. Two cases could not be matched with controls, and 18 families wished not to be interviewed. Of the nine interviews where only partial information was obtained, five were conducted with a surrogate respondent (one foster parent, two stepparents, and two adoptive parents), precluding for these cases collection of data pertaining to the prenatal and preconception periods.

Control selection: results of random digit dialing

Selection and interviewing of controls began in May 1983 and continued through June 1984, a time period coinciding with case interviewing. Of the 2,225 telephone numbers called (table 2), 834 (37.5 percent) were nonworking, 246 (11.1 percent) were nonresidential, and 150 calls (6.7 percent) could not be completed in seven attempts. Among the 995 completed residential calls (44.7 percent of all calls), 224 resulted in a refusal to participate, while 512 calls were to residences with no eligible children. The 259 calls completed to eligible homes resulted in the completion of 205 interviews; the results of 193 were used in case-control comparisons, since 12 control families were interviewed but the corresponding cases were not. The frequency of reliance on surrogate respondents in the control group was similar to that in the case group (see table 1 footnotes). Unless otherwise indicated, the matched analysis was based on 110 cases and 193 controls (27 pairs and 83 triplets).

Nonoccupational case-control differences

As was discussed in review papers by Gold (49) and Greenberg and Shuster (50) and noted recently by Nasca et al. (35), the only consistently demonstrated risk factors for childhood central nervous system tumors are age, sex, and race. Because cases and controls were matched on these factors and because cases and controls were generally similar with regard to other potentially important factors (such as parental age, birth weight, mother and/or child exposure to x-rays, domestic use of pesticides, parental occupational exposure to pesticides, and direct or indirect maternal exposure to tobacco smoke), only unadjusted odds ratios are presented. Although controls were more likely than cases to be first

TABLE 1

Selected characteristics of cases in a study of parental occupation and childhood brain tumors, central Ohio, 1983–1984

Characteristic	Total case series*		Subset with completed interviews†	
	No.	%	No.	%
Sex				
Male	99	65.6	74	67.3
Female	52	34.4	36	32.7
	151	100.0	110	100.0
Race				
White	142	94.0	106	96.4
Nonwhite	9	6.0	4	3.6
	151	100.0	110	100.0
Age (years) at diagnosis				
0–4	47	31.1	38	34.5
5–9	51	33.8	37	33.6
10–14	39	25.8	25	22.7
15–19	14	9.3	10	9.1
	151	100.0	110	99.9
Histopathology				
Astrocytoma	46	30.5	32	29.1
Medulloblastoma	34	22.5	30	27.3
Unspecified glioma	18	11.9	13	11.8
Ependymoma	9	6.0	6	5.5
Glioblastoma multiforme	6	4.0	4	3.6
Sarcoma	3	2.0	2	1.8
Other	12	7.9	10	9.1
Not microscopically confirmed‡	23	15.2	13	11.8
	151	100.0	110	100.0

* As determined from review of tumor registry files for the period January 1, 1975–December 31, 1982.

† Includes nine interviews where only partial information could be obtained, including five interviews with surrogate respondents (see text).

‡ Tumor registry records indicated that these tumors were judged to be inoperable.

TABLE 2

Results of control selection by random digit dialing, in a study of parental occupation and childhood brain tumors, central Ohio, 1983–1984

Outcome	No. of calls	% of all calls	% of residential calls only
All calls			
Residential number	995	44.7	
Nonworking number	834	37.5	
Nonresidential number	246	11.1	
No answer after seven attempts	150	6.7	
Total	2,225	100.0	
Residential calls only			
No eligible children	512	23.0	51.5
Residence with eligible children*	259	11.6	26.0
Refusal†	224	10.1	22.5
Total	995	44.7	100.0

* Among the 259 homes with eligible children, 205 interviews were conducted; the results of 193 were used in the analysis.

† Refusals occurred prior to determination of the household's eligibility.

births and case parents tended to be less educated than their control counterparts, the magnitudes of crude and adjusted odds ratios for the parental occupation variables entered into regression equations were similar.

Case-control comparisons by paternal occupation

Table 3 summarizes the results of odds ratio estimation for the occupational categories (44) having at least 10 subjects. Several odds ratios were elevated, notably those in the preconception period corresponding to paternal employment in agriculture (odds ratio (OR) = 2.7, 95 percent confidence interval (CI) 0.8–9.1), benchwork occupations (OR = 2.7, 95 percent CI 0.8–9.0), and transportation (OR = 2.3, 95 percent CI 0.7–8.1). For each of these occupational categories, the effect was greatest in the preconception period and smallest in the postnatal period (range of odds ratios in the postnatal period, 0.9–1.8), while elevated odds ratios of intermediate magnitude were seen in the prenatal period (range, 1.6–2.1). Modestly elevated odds ratios in the preconception period were found for processing occupations (OR = 1.8, 95 percent CI 0.6–5.3) and machine trades (OR = 1.6, 95 percent CI 0.7–3.7), although here the pattern referred to above was not apparent. With the exception of the reference group, the number of case fathers in each category was relatively small, ranging from four to 20, thus accounting for the imprecision seen in the point estimates. Note that all confidence intervals in table 3 include 1.0.

Case-control comparisons by paternal industry

Results of odds ratio estimation by paternal industry of employment (45) are summarized in table 4. Several odds ratios were again elevated here, notably three in the preconception period corresponding to paternal jobs in agriculture (OR = 2.8, 95 percent CI 0.9–8.4), construction (OR = 1.8, 95 percent CI 0.6–5.1), and metal industries (OR = 3.3, 95 percent CI 1.3–8.5). The pattern seen in table 3 of greatest excess risk in the preconception period and intermediate and lowest risks in the prenatal and postnatal periods, respectively, was repeated. Elevated odds ratios were also seen for paternal jobs in the food and tobacco industry in two of the three time periods and for paternal jobs in the rubber/plastics/synthetics industry (postnatal period only). Again, relatively small numbers of case fathers fell into the various industry categories, accounting for the imprecise point estimates. Note that all but one confidence interval in table 4 include 1.0.

Case-control comparisons by maternal occupation

For all time periods, more than 80 percent of maternal jobs classified by standard occupational groupings (44) fell into either the reference category or service occupations. The extreme sparseness of these data permitted odds ratio estimation for just three categories (service, processing, and benchwork) and accounts for the unstable excess risk estimates. Among the seven occupation- and time-specific odds ratios computed here (table 3), one was elevated (processing occupations: OR = 2.6, 95 percent CI 0.8–8.6, postnatal period).

Case-control comparisons by maternal industry

More than half of the maternal jobs classified according to the *Standard Industrial Classification Manual* (45) were considered low-exposure (52–75 percent of such jobs). Other reported industry affiliations included food and tobacco (4–13 percent), machinery (4–7 percent), and medicine and science (7–14 percent).

The sparseness of these data permitted odds ratio estimation for only five industry categories (machinery, food and tobacco, textiles, medicine and science, and entertainment and recreation). As table 4 shows,

TABLE 3

Results of odds ratio estimation: parental occupation, by DOT category, central Ohio, 1983–1984†*

DOT category	Postnatal			Prenatal			Preconception		
	No. of case parents	OR*	95% CI*	No. of case parents	OR	95% CI	No. of case parents	OR	95% CI
Paternal									
Reference group‡	42	1.0		50	1.0		48	1.0	
Service	8	0.8	0.3–2.1	6	0.6	0.2–1.9	5	0.4	0.1–1.4
Agriculture	4	0.9	0.3–2.9	4	1.6	0.4–6.1	6	2.7	0.8–9.1
Processing	7	1.4	0.5–3.7	5	1.2	0.4–1.3	7	1.8	0.6–5.3
Machine trades	18	1.3	0.6–2.5	10	1.2	0.5–2.9	11	1.6	0.7–3.7
Benchwork	13	1.8	0.8–3.9	7	2.1	0.7–6.2	6	2.7	0.8–9.0
Structural work	20	1.3	0.6–2.8	14	1.2	0.6–2.4	14	1.3	0.7–2.6
Motor freight and transportation, NEC*	9	1.7	0.7–4.5	7	1.8	0.6–5.4	6	2.3	0.7–8.1
Maternal									
Reference group‡	78	1.0		96	1.0		87	1.0	
Service	17	0.9	0.5–1.7	7	0.8	0.3–2.3	12	1.0	0.5–1.7
Processing	7	2.6	0.8–8.6	1			2		
Benchwork	6	0.7	0.3–1.9	3	0.7	0.2–2.7	6	1.4	0.5–4.3

* DOT, *Dictionary of Occupational Titles* (44); OR, odds ratio; CI, confidence interval; NEC, not elsewhere classified.

† Odds ratios were not computed if there were less than 10 subjects in a category.

‡ Includes professional, technical, and managerial occupations; clerical and sales occupations; packaging and materials handling occupations; and retired or unemployed persons, as well as those having unknown or unclassifiable occupations.

TABLE 4

Results of odds ratio estimation: parental industry of employment, by SIC grouping, central Ohio, 1983–1984†*

SIC category	Postnatal			Prenatal			Preconception		
	No. of case parents	OR*	95% CI*	No. of case parents	OR	95% CI	No. of case parents	OR	95% CI
Paternal									
Reference group‡	24	1.0		25	1.0		25	1.0	
Agriculture, forestry, and fishing	6	1.0	0.3–2.8	6	2.0	0.6–6.6	8	2.8	0.9–8.4
Construction	10	0.9	0.4–2.3	9	1.6	0.6–4.4	8	1.8	0.6–5.1
Paper and wood	2			2			3	1.4	0.3–5.9
Glass, clay, and stone	1	0.3	0.1–2.2	1			2	0.6	0.1–3.3
Metal	16	1.7	0.7–3.7	10	2.0	0.8–5.1	13	3.3	1.3–8.5
Machinery	10	0.7	0.3–1.8	11	1.1	0.4–2.7	9	0.9	0.3–2.5
Transportation	22	1.2	0.8–1.8	15	1.7	0.7–3.9	13	1.3	0.6–3.2
Food and tobacco	9	1.1	0.4–3.0	11	2.3	0.8–6.1	9	1.8	0.7–4.7
Rubber, plastics, and synthetics	7	1.8	0.6–5.4	3			3		
Fuel	2	0.7	0.1–3.7	2			3		
Medicine and science	6	1.1	0.3–3.4	4	1.3	0.3–5.6	4	1.3	0.3–5.8
Maternal									
Reference group‡	62	1.0		81	1.0		75	1.0	
Machinery	8	0.9	0.4–2.2	4	0.8	0.3–2.7	7	1.6	0.6–4.4
Food and tobacco	16	1.5	0.7–3.0	9	1.8	0.7–4.6	9	1.2	0.5–2.8
Textiles	1	0.3	0.1–2.1	0			1		
Medicine and science	9	0.5	0.2–1.2	8	0.9	0.3–2.3	8	1.0	0.4–2.6
Entertainment and recreation	5	1.3	0.4–4.1	0			0		

* SIC, standard industrial classification (45); OR, odds ratio; CI, confidence interval.

† Odds ratios were not computed if there were less than 10 subjects in a category.

‡ Low-exposure industries (business, law, sales, etc.), as defined by Hoar et al. (37); also included are retired or unemployed persons or persons with unclassifiable or unknown industrial affiliations.

none of the computed odds ratios were notably elevated, except perhaps the food-and-tobacco odds ratio of 1.8 seen in the prenatal period (95 percent CI 0.7–4.6).

Job cluster analysis

Paternal job clusters. As table 5 shows, it was possible to examine case-control differences in paternal job clusters for 16 of the 22 clusters. Notably elevated odds ratios in at least two time periods were seen to correspond to four clusters (3, 6, 20, and 22 + 23 + 24). To facilitate interpretation of the job cluster results, we constructed table 6, showing the degree-of-exposure designators for the clusters associated with excess risk. For clusters 3 and 20, two of the three estimated confidence intervals excluded 1.0. The two highest odds ratios corresponded to cluster 20 (OR = 4.7, 95 percent CI 1.2–18.7, for the prenatal period; OR = 7.0, 95 percent CI 1.4–34.6, for the preconception period); the previously noted pattern of greatest excess risk in the preconception period as seen in tables 3 and 4 was apparent here as well. This particular cluster consists of jobs linked with moderate-to-heavy exposure to (unspecified) aromatic and aliphatic hydrocarbons, metals, and minerals (i.e., the agent group degree-of-exposure designator was greater than or equal to 2.0). Industries represented in cluster 20 include mining, metal, transportation, fuel, and the arts. Cluster 3, associated with notably elevated odds ratios in all three time periods, is dominated by jobs in agriculture and construction, although transportation, fuel, medicine and science, and entertainment and recreation are also represented; linked moderate-to-heavy exposures here include aromatic hydrocarbons and nonionizing radiation.

Cluster 6, associated with two notably elevated odds ratios, is dominated by metal-related jobs like cluster 20 but also includes jobs linked with moderate-to-heavy exposure to aromatic hydrocarbons (graphic art; photoengraving; fur working; and repair of plastics, synthetics, rubber, and related products). Cluster 22 + 22 + 24 (with odds ratios ranging from 1.8–2.7) is dominated by paint-related jobs and by processing jobs in the following industries: textiles; chemicals, drugs, and paints; and rubber, plastics, and synthetics. Moderate-to-heavy exposures in this cluster include aromatic amino compounds; aromatic and aliphatic hydrocarbons; alcohols, glycols, acids, and derivatives; esters; metals; minerals; inorganic halogens; and unspecified organic and inorganic compounds.

Maternal job clusters. Because of small numbers of subjects in most groupings here, only four clusters (3, 18, 22, 22 + 23 + 24) could be analyzed separately by time period (table 7). Notably elevated odds ratios corresponded to cluster 22 + 23 + 24 for all three time periods (range of odds ratios, 1.7–2.2; lower limit of 95 percent confidence intervals, 0.8–0.9) and to cluster 3 for one period (preconception OR = 2.1, 95 percent CI 0.6–7.3). Moderate-to-heavy exposures linked with these clusters have been described above.

Inferred occupational exposure to N-nitroso- and related compounds

Frequency of moderate-to-heavy occupational exposure to the selected compounds among fathers of cases was low in both the prenatal and preconception periods, rarely going higher than 4 percent; for almost one third of the chemicals, no moderate-to-heavy job exposure link was present in any time period. The presence of such a job exposure link occurred more often during the postnatal period but was never higher than 16.7 percent for any of the 35 agents. A similar pattern was seen among fathers of controls. Maternal jobs were much less likely to have been linked with *N*-nitroso compounds in any of the time periods.

Results of agent-specific odds ratio estimation are summarized in table 8 for paternal *N*-nitroso exposure only. Because

TABLE 5

Results of odds ratio estimation: paternal job cluster analysis, by time period, central Ohio, 1983–1984

Hsieh et al. (38) cluster	Postnatal			Prenatal			Preconception		
	No. of case fathers	OR*	95% CI*	No. of case fathers	OR	95% CI	No. of case fathers	OR	95% CI
0 + 1†	42	1.0		37	1.0		37	1.0	
2	7	2.9	0.9–9.4	3			3		
3	16	2.4	1.1–5.4	12	2.0	0.8–5.1	13	3.2	1.1–8.8
4	2	0.3	0.1–1.6	1	0.2	0.02–1.5	0		
5	3	1.1	0.3–4.6	5			4		
4 + 5	5	0.5	0.2–1.6	6	0.7	0.2–2.2	4	0.5	0.2–1.7
6	9	2.7	1.02–7.9	3			5	2.4	0.7–8.6
7	5	1.2	0.4–3.7	4	1.0	0.3–3.3	4	1.0	0.3–3.4
6 + 7	14	1.9	0.9–4.1	7	1.1	0.4–2.8	9	1.5	0.6–3.7
10 + 11 + 12	4	1.2	0.3–4.0	4	1.6	0.4–6.0	4		
16	10	1.0	0.4–2.4	7	1.1	0.4–2.9	5	0.7	0.2–2.1
17	4	0.6	0.2–2.2	3	0.6	0.2–2.4	3	0.5	0.1–2.0
16 + 17	6	0.8	0.3–2.5	4	0.8	0.2–2.6	4	0.7	0.2–2.4
18	5	1.4	0.4–4.4	4	1.2	0.3–4.5	3	0.9	0.2–4.0
20	9	2.1	0.8–5.5	8	4.7	1.2–18.7	8	7.0	1.4–34.6
22	9	2.3	0.8–6.2	4	1.5	0.4–6.0	2		
22 + 23 + 24	12	2.7	1.1–6.8	6	1.8	0.5–6.2	5	2.4	0.7–7.8

* OR, odds ratio; CI, confidence interval.

† Low-exposure reference category, as defined by Hsieh et al. (38).

TABLE 6

Degree-of-exposure scores for parental occupational clusters associated with elevated childhood brain tumor risk, central Ohio, 1983–1984*

Agent group	Cluster			
	3	6	20	20 + 23 + 24
Organic compounds				
Aromatic amino compounds	0.2	0	0.8	2.7
Aromatic nitro compounds	0.2	0.2	0	1.5
Aromatic halogens	0	0.1	0	1.8
Aromatic azo compounds	0.2	0.3	0	1.4
Phenols	0.2	0.7	1.6	1.8
Aromatic hydrocarbons, NOS†	2.3	2.1	2.7	2.4
Alicyclic halogens	0.1	0.1	0	0.6
Alicyclic hydrocarbons, NOS	1.0	0.6	0.5	1.9
Alkylating agents	0.2	1.2	0.7	1.4
Aliphatic halogens	0.4	0.2	1.0	1.8
Aliphatic nitro compounds	0	0	0	0.4
Alcohols, glycols, acids, and derivatives	0.3	1.9	1.6	2.2
Aldehydes, ketones, ethers, and derivatives	0.3	0.1	0.2	1.9
Esters	0.2	0.1	0.2	2.2
Aliphatic hydrocarbons, NOS	1.7	1.8	2.6	2.4
Other organic compounds, NOS	0.2	0.5	1.2	2.3
Inorganic compounds				
Metals, metalloids, and their compounds	0.9	2.3	2.9	2.7
Minerals	0.2	1.5	2.0	2.1
Inorganic halogens	0.5	1.2	1.5	2.0
Inorganic compounds, NOS	0.6	1.6	1.8	2.1
Physical agents				
Nonionizing radiation	2.4	0.5	0.5	0.8
Ionizing radiation	0.8	0	1.8	1.8
Dusts	0.2	0.4	0	0.6
Other physical agents	0.6	0	0.2	1.2

* As defined by Hsieh et al. (38), a value of 1 denotes light exposure, 2 denotes moderate exposure, and 3 denotes heavy exposure.

† NOS, not otherwise specified.

exposure frequencies for many of the *N*-nitroso and/or related compounds were quite low, it was possible to compute odds ratios for only 17 of the 35 agents selected. Except for the prenatal and preconception picric acid results and the preconception aniline result, the notably elevated odds ratios were seen here in the postnatal period. In addition to the *N*-butylamine and 4-nitrodiphenyl results, four of the elevated odds ratios corresponded to aniline-derived aromatic amino compounds and two corresponded to naphthalene-derived aromatic amino compounds. Although these results suggest that the highest relative risk occurs in the postnatal period, in contrast to the results set forth in tables 4, 5, and 7, small numbers precluded odds ratio estimation for all agents for all of the periods. Note, however, that the pattern of greatest excess risk in the preconception period is demonstrated for picric acid, an aromatic nitro compound (OR = 5.7, 95 percent CI 1.4–23.2, preconception period). Note also that, unlike the other results, most of the elevated odds ratios in table 8 have confidence intervals that exclude (or nearly exclude) 1.0.

For maternal occupational exposures to *N*-nitroso compounds, it was possible to

TABLE 7

Results of odds ratio estimation: maternal job cluster analysis, by time period, central Ohio, 1983–1984

Hsieh et al. (38) cluster	Postnatal			Prenatal			Preconception		
	No. of case mothers	OR*	95% CI*	No. of case mothers	OR	95% CI	No. of case mothers	OR	95% CI
0 + 1†	76	1.0		71	1.0		70	1.0	
3	8	1.4	0.5–3.7	5	1.7	0.5–5.6	5	2.1	0.6–7.3
18	5	0.7	0.2–1.9	5	0.7	0.2–2.0	5	0.8	0.3–2.6
22	15	1.8	0.8–3.9	12	2.1	0.9–5.1	12	2.2	0.9–5.4
22 + 23 + 24	16	1.7	0.8–3.6	13	2.1	0.9–4.8	13	2.2	0.9–5.1

* OR, odds ratio; CI, confidence interval.

† Low-exposure reference category, as defined by Hsieh et al. (38).

compute agent-specific odds ratios for only 13 agents (postnatal period only). None of the computed odds ratios here were notably elevated (range, 0.7–1.5).

DISCUSSION

In this study, data analysis revealed a pattern of greatest excess risk for paternal jobs held prior to conception (tables 3–5). Although the odds ratios would not be considered statistically significant in conventional terms, these findings nevertheless provide empirical human evidence consistent with the hypothesis that paternal germ cell damage may manifest years later as cancer in the offspring (13). Results of one notable animal experiment lend credence to a prezygotic paternal role. In the study by Tomatis et al. (51), male rats were given a single dose of ethylnitrosourea prior to mating with untreated females. In addition to lowered fertility among the females mated with the treated males and increased preweaning mortality among the offspring, the progeny demonstrated an increased incidence of nervous system tumors as compared with controls (5.6 percent vs. 1.9 percent; $p = 0.08$).

Other animal studies support the prenatal exposure hypothesis, i.e., that some childhood cancers may result from prenatal exposure(s) of the embryo/fetus (9, 23, 36). Such studies (52–54), including the one by Druckrey et al. (55) conducted more than 20 years ago, have demonstrated the ability of *N*-nitroso compounds to induce nervous system tumors in the offspring of rats as a result of direct exposure of the mother (and thus, indirectly, exposure of the embryo/fetus). A role for paternal exposure (via soiled work clothing, for example) is less clear, although a father or cohabitor may be responsible for such exposures, as has been previously shown for lead, polychlorinated biphenyls, and dioxin (56).

To a limited extent, our findings are consistent with the results of other epidemiologic studies in this area. Positive associa-

TABLE 8

Results of odds ratio estimation: inferred moderate-to-heavy occupational exposure of fathers to N-nitroso and related compounds, central Ohio, 1983–1984

Agent group	Agent	Postnatal		Prenatal		Preconception	
		OR*	95% CI*	OR	95% CI	OR	95% CI
Aromatic amino compounds							
Aniline derivatives	Aniline	1.5	0.7–3.2	1.4	0.4–5.6	3.1	0.8–11.8
	4-Aminodiphenyl	4.0	1.1–14.2				
	Benzidine	4.3	1.3–13.8				
	Magenta	3.9	1.1–13.8				
	Auramine	3.4	0.9–12.7				
	2-Chloroaniline	0.8	0.4–1.7	0.5	0.4–5.8	0.4	0.1–2.0
Naphthalene derivatives	1-Naphthylamine	4.4	1.2–15.5				
	2-Naphthylamine	3.8	1.3–10.5				
	8-Hydroxyquinoline	0.7	0.3–1.7	0.7	0.2–2.6	0.9	0.2–3.0
Aliphatic amines/amides	*N*-Butylamine	2.4	0.7–7.7				
	Ethanolamine	1.4	0.6–3.3				
	Ethylenediamine	1.5	0.6–3.9	0.6	0.1–2.9		
	N,N-Dimethylformamide	1.1	0.3–4.0				
	Thioacetamide	1.0	0.3–3.0				
Aromatic nitro compounds	Nitrobenzene	1.6	0.4–6.1				
	4-Nitrodiphenyl	4.0	1.1–14.2				
	Picric acid	1.8	0.7–4.5	2.1	0.5–8.2	5.7	1.4–23.2

* OR, odds ratio; CI, confidence interval.

tions between childhood central nervous system tumors and paternal jobs in agriculture (tables 3 and 4), transportation (table 3), and construction (table 4 and the cluster 3 results) have been previously reported (25, 27, 33, 57), although not in all earlier studies (1, 5, 7, 9, 25, 27). Results of the Gold et al. (58) study indicated no case-control differences with respect to paternal occupational exposure to "chemicals," although they did find excess risk associated with farm residence and with childhood exposure to sick animals and household insecticides. Previously reported associations for paternal jobs in construction per se are limited to the studies by West and Leviton (27) and Wilkins and Koutras (33). In the case-control study of childhood central nervous system tumors reported by Johnson and Spitz (37), the odds ratio corresponding to paternal employment as a construction electrician exceeded 10 (95 percent CI 1.2–86.3).

As inferred from the job cluster analysis (tables 5–7), parental jobs associated with excess risk were also found to be linked with occupational exposure to metals (previously reported by Wilkins and Koutras (33); see also table 4), paints (previously reported by Hemminki et al. (7) and Peters et al. (6)), and unspecified aromatic and aliphatic hydrocarbons (previously reported by West and Leviton (27), Gold et al. (9), Johnson et al. (19), and Fabia and Thuy (1)). The finding of excess risk associated with parental occupational exposure to aromatic amino and aromatic nitro compounds has not been reported previously and therefore requires confirmation, particularly since aromatic amines are not associated with transplacental activity or linked with nervous system tumors, as is also the case with *N*-butylamine, 4-nitrodiphenyl, and picric acid.

The meaningfulness of the results reported here depends heavily on the validity of the Hoar et al. job exposure matrix. Although this particular matrix has been previously used in studies of both adult (59) and childhood (12) cancers, uncertainties remain concerning its validity. These uncertainties stem from the following characteristics of the system: a singular focus on known or suspected carcinogens, lack of validation of the exposure links and the associated exposure intensity estimates, and sole reliance on review of scientific and technical literature that spans the period 1962–1979. In the only attempt to evaluate the Hoar et al. job exposure matrix that we are aware of, it demonstrated poor sensitivity (≤35 percent) but rather high specificity (≥80 percent) as compared with self-reports of occupational benzene or asbestos exposure (60). Whether the Linet et al. (60) sensitivity/specificity analysis provides any meaningful insight into the operating characteristics of the Hoar et al. (39) system rests heavily on the appropriateness of treating self-reported occupational exposure data as the "gold standard."

One aspect of exposure assessment that needs special attention in future studies concerns the timing of exposure insofar as this relates to the particular phenomenon under study, and whether maternal or paternal exposures are more important from an etiologic point of view. In the study reported here, and in most other studies in this area where personal interviews were conducted, investigators have operationally addressed the question of exposure timing by obtaining exposure data from both parents for all potentially relevant time periods—i.e., before, during, and after the index pregnancy. This approach has been motivated in part by the lack of understanding of the precise biologic mechanisms involved, although a sound biologic rationale borne of the transplacental carcinogenesis literature does exist (40, 52, 61–64).

While there are study design limitations and interpretational dilemmas, the results of this study and others (6, 15, 19, 27, 33, 37) are sufficient to warrant further investigation. In future studies, exposure assessment, including validation of self-reported

employment and exposure histories, is perhaps in greatest need of refinement—although case definition, particularly in the context of studies that focus on childhood brain tumors, also needs careful consideration. Histology-specific analyses, in addition to subgroup analyses specific for anatomic site, age at diagnosis, etc., may be required to reveal what may be unique exposure-disease associations heretofore masked by the etiologic heterogeneity of previously assembled case series. For such analyses, large multi-institutional efforts may be needed. We also acknowledge that in the present study many odds ratios were computed. raising concern about the problem of multiple comparisons. Although we have focused on the magnitude of the effect estimator (and not on the degree of statistical significance), it must be allowed that some odds ratios may have been elevated by chance. However, the repeated pattern of greatest excess risk in the preconception period mitigates against this explanation somewhat, as does the fact that the estimation was done on a priori grounds, not a posteriori ones.

The results presented here do not provide conclusive evidence that paternal occupational exposures induce childhood nervous system tumors. Limitations that detract from the significance of our findings have been noted above. Although childhood cancer is a statistically rare event, the emotional and psychologic toll on its victims and their families cannot be quantified, and the estimable years of life lost is significant. Any clues that may further an understanding of its pathogenesis must therefore be vigorously pursued.

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