Parental Occupation and Childhood Cancer: Review of Epidemiologic Studies

by David A. Savitz* and Jianhua Chen*

Parental occupational exposures might affect childhood cancer in the offspring through genetic changes in the ovum or sperm or through transplacental carcinogenesis. The 24 published epidemiologic studies of this association have all used case-control designs, with controls generally selected from birth certificates or from general population sampling. Occupational exposures were inferred from job titles on birth certificates or through interviews. A large number of occupation-cancer associations have been reported, many of which were not addressed or not confirmed in other studies. Several associations have been found with consistency: paternal exposures in hydrocarbon-associated occupations, the petroleum and chemical industries, and especially paint exposures have been associated with brain cancer; paint exposures have also been linked to leukemias. Maternal exposures have received much less attention, but studies have yielded strongly suggestive results linking a variety of occupational exposures to leukemia and brain cancer. The primary limitations in this literature are the inaccuracy inherent in assigning exposure based on job title alone and imprecision due to limited study size. Although no etiologic associations have been firmly established by these studies, the public health concerns and suggestive data warrant continued research.

Introduction

In spite of numerous epidemiologic studies of parental occupation and childhood cancer, no clear causal associations have been established (1,2). In fact, the only established human carcinogen that acts through either parent is diethylstilbestrol, a drug administered during pregnancy that causes vaginal adenocarcinoma in female offspring (3). It happens that the resulting vaginal cancer does not appear during childhood, but this agent establishes the plausibility of transplacental exposures affecting human cancer risk. In utero exposure to diagnostic X-rays is strongly suspected of causing leukemia during childhood (4), but the association remains controversial (5).

The evidence that parental occupational exposures can adversely affect reproductive outcomes other than cancer is persuasive (1,6). Exposures to males can cause infertility (7) and possibly miscarriages among wives of exposed workers (8,9). Pregnant women who work with anesthetic gases appear to have an excess of miscarriages (10,11) as do nurses exposed to chemotherapeutic drugs used in cancer treatment (12). Studies of parental occupation and childhood cancer are predicated on the limited evidence linking other parental exposures (drugs, X-rays) to childhood cancer combined with the stronger indications that agents in the workplace can adversely affect reproduction (13).

Potential mechanisms for an effect of parental occupational exposures specifically on childhood cancer are speculative. Preconception maternal exposures might have genetic effects that alter the offspring's susceptibility to cancer, although the ovum appears to be relatively protected from exogenous agents (14).

Transplacental carcinogenesis is a more likely mechanism through which in utero exposures would influence the later development of cancer. As noted earlier, diethylstilbestrol remains the only established human transplacental carcinogen, but extensive laboratory evidence (15) supports the plausibility of environmental agents operating in this manner and suggests that prenatal exposures may be more potent than postnatal exposures. The evidence for transplacental toxicity is clear for maternal exposure to teratogens such as lead and alcohol (14). Enhanced susceptibility to cancer during childhood could be viewed as a type of congenital anomaly produced by maternal exposure to workplace teratogens. Nonetheless, a series of assumptions is required to argue for the plausibility of an etiologic role of maternal occupational exposures in childhood cancer.

The potential mechanisms through which male occupational exposures might affect the offspring's risk of cancer are far more tenuous. One possible pathway is for the father to bring toxic exposures into his home (16) and thereby expose his wife and, transplacentally, the fetus. Such an indirect route could only occur for nonvolatile chemical agents such as lead. Whether the

*Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC 27599.

Address reprint requests to D. A. Savitz, Department of Epidemiology, CB #7400, School of Public Health, University of North Carolina, Chapel Hill, NC 27599.
dose of a toxic agent would be sufficiently large to reach the wife and then the fetus in appreciable quantities is questionable.

A biologically interesting but far more speculative mechanism is a genetic alteration in the father's sperm that would transmit an enhanced cancer susceptibility to his child. Genetic syndromes, which include specific types of childhood malignancies such as certain forms of retinoblastoma or Wilms' tumor, are well documented (17), and the paternal genome clearly can contribute to this risk. Sperm are genetically susceptible to environmental agents (18). Epidemiologic evidence for parentally mediated reproductive effects other than infertility, however, is quite limited. No paternal exposure (drugs, tobacco, radiation, or environmental chemicals) has been proven to cause miscarriage, congenital defects, or childhood cancer (6,13). Laboratory evidence suggests that paternal exposures to rats can affect fetal loss and malformations (19), growth (20), and even subsequent cancer risk (21) without altering fertility. Examination of exposures that might genetically alter sperm to enhance the risk of cancer in the offspring of humans thus has some experimental basis, but a well-defined biological basis for paternal exposures increasing the risk of childhood cancer is absent.

In spite of a somewhat tenuous biological rationale, the association of parental occupation and childhood cancer has received substantial interest. The methods and results of the 24 epidemiologic evaluations of parental occupation and childhood cancer that were found in the literature up to October 1989 (22-45) are reviewed. The literature is essentially a collection of unrelated empirical observations that are not well-suited to a condensed narrative summary (2), so detailed tables have been provided. Relative to an earlier review (46), the volume of literature has grown and a more systematic approach to the classification of study results was developed. As studies proliferate, it will be important to identify those associations that are sufficiently consistent and plausible to deserve the intensive effort that will ultimately be required to establish or refute suggestions of causality.

Methods of Review

All published literature that directly assessed parental occupation and any form of childhood cancer in humans was included. Although the primary interest was on chemical and physical hazards in the workplace, occupations not likely to incur such exposures were also considered. Study methodologies were summarized and results were tabulated according to the exposed parent (father, mother), the type of childhood cancer studied (total, leukemias and lymphomas, nervous system, and urinary tract), and the nature of the occupational exposure (hydrocarbons, metals, etc.). Odds ratios addressing similar associations were tabulated in chronological order by the year of publication.

Results

Study Methods

Table 1 summarizes the constitution of the study groups, exposure definitions, and confounders included in these 24 studies. Interest in this topic has recently expanded: only two of the studies were published before 1980 versus 15 in 1984 or later. All of the studies used case-control sampling, with the proportionate mortality analysis of Sanders et al. (26) interpretable as a case-control study in which the control group consists of all decedents (47).

The age range of cancer cases varied markedly across studies, with upper age limits ranging from 1 (29) to 24 years old (36). Vianna et al. (29) postulated that the earliest cancers are more likely to be affected by in utero exposures. Most studies have been conducted in the United States, with one each in Canada, Finland, England and Wales, the Netherlands, and China (Table 1). Although the biological relationships of interest would not be expected to differ as a function of geographic
Table 1. Case and control groups, exposure definition, and confounders in studies of parental occupation and childhood cancer.

| Reference | Study location and study period | Case group | Upper age limit, years | Number of cases | Source of control information | Source of exposure information | Time period of exposure | Potential confounders considered |
|-----------|---------------------------------|------------|------------------------|----------------|------------------------------|-------------------------------|--------------------------|----------------------------------|
| Total cancers |                                 |            |                        |                |                              |                               |                          |                                  |
| (22) Quebec, 1965–1970 | Cancer deaths | 4          | 386                    | Birth certificates | Father's occupation on birth certificate | At birth | Parents' ages, residence |
| (23) Massachusetts, 1947–1957, 1963–1967 births | Cancer deaths | 14         | 692                    | Birth certificates | Father's occupation on birth certificate | At birth | Parents' ages, sex, and race of child |
| (24) Houston area, 1976–1977 | Cancer cases | 15         | 296                    | Clinic records, case parent siblings, neighborhood | Parents' occupational histories from interview | Year before birth through diagnosis | Father's age, parents' education |
| (25) Finland, 1959–1975 | Cancer cases | 14         | 948                    | Birth certificates | Parents' occupation in welfare center records | During pregnancy | Parents' ages, birth order, birth weight, residence |
| (26) England and Wales, 1959–1963, 1970–1972 | Cancer deaths | 14         | 6920                   | All childhood deaths | Father's occupation on child's death certificate | At death | Social class |
| (27) Houston area, 1976–1977 | Cancer cases | 15         | 298                    | Clinic records, case parent siblings, neighborhood | Parents' occupational histories from interview | Year before birth | None |
| Leukemias and lymphomas |                                 |            |                        |                |                              |                               |                          |                                  |
| (28) Baltimore SMSA, 1965–1974 (brain), 1969–1974 (leukemia) | Brain tumor and leukemia cases | 19         | 43                      | Birth certificates, other cancer cases | Parents' occupational histories from interview | Before birth through diagnosis | Sex, year of birth, race |
| (29) New York State (outside New York City), 1949–1978 | Acute leukemia cases | 1          | 65                      | Birth certificates | Parents' occupational histories from interview | Before birth | Year of birth, sex, race, county, parents' ages, birth order, maternal education, X-rays, other exposures |
| (30) California, 1975–1980 | Leukemia cases | 15         | 255                    | Birth certificates | Father's occupation on birth certificate | At birth | Parents' ages, child's race, sex, and birth order |
| (31) Netherlands, 1973–1979 | Acute lymphocytic leukemia cases | 14         | 519                    | Population-based | Parents' occupational histories from questionnaire | During pregnancy and 1 year before birth | Age, sex, residence, birth order, social class |
| (32) Los Angeles County, 1980–1984 | Acute leukemia cases | 10         | 123                    | Case friends and random digit dialing | Parents' occupational histories from interview | 1 year before conception to 0.5 or 1 year before diagnosis | Parents' smoking, drinking, diet, mother's medications, child's age, sex, race, ultrasound, X-ray exposure |
| (33) Shanghai, China, 1974–1986 | Leukemia cases | 15         | 309                    | Neighborhood | Parents' occupational histories from interviews | Before conception and during pregnancy | Age, sex, birth weight, birth order, residence, X-rays, medications, mother's age at menarche |
| (34) U.S. and Canada, 1980–1984 | Acute nonlymphocytic leukemia cases | 18         | 204                    | Random digit dialing | Parents' occupational histories from interview | Lifetime | Age, race |

(continued)
Table 1. Continued.

| Reference | Study location and study period | Case group | Upper age limit, years | Number of cases | Source of exposure information | Time period of exposure | Potential confounders considered |
|-----------|---------------------------------|------------|------------------------|-----------------|-------------------------------|-------------------------|----------------------------------|
| (53)      | Los Angeles County, 1972–1977    | Brain tumor cases | 9                      | 98              | Case friends, neighbors       | Year before birth through diagnosis | Mother's smoking, drugs, alcohol, hair dyes, foods during pregnancy |
| (36)      | Los Angeles County, 1972–1977    | Brain tumor cases | 24                     | 226             | Case friends, neighbors       | Before birth to before diagnosis | Numerous parent and child characteristics |
| (37)      | Texas, 1964–1978                 | Neuroblastoma deaths | 14                     | 157             | Birth certificates            | At birth                  | Parents' ages, residence, prenatal care, marital status, child's sex, ethnicity |
| (38)      | Western Washington State, 1978–1981 | Brain tumor cases | 16                     | 51              | Random digit dialing and area sampling | 1 yr. before birth to diagnosis | Parents' ages, smoking, drinking patterns, mother's exposure to chemicals, child's sex, age, race |
| (39)      | Texas, 1964–1980                 | Intracranial and spinal cord tumor deaths | 15                     | 499             | Birth certificates            | At birth                  | Child's age, sex, race, birth weight, birth order, gestational age, parents' ages, residence, prenatal care, etc. |
| (40)      | Ohio, 1959–1978                  | Brain tumor deaths | 19                     | 491             | Birth certificates            | At birth                  | Sex, race, year of birth, parents' ages, birth weight, birth order, county |
| (41)      | New York State (outside New York City), 1968–1977 | Central nervous system tumor cases | 15                     | 338             | Birth certificates            | At birth and at diagnosis | Child's age, sex, race, birth weight, birth order, county |
|           |                                 |            |                        |                 |                               |                         |                                  |
| (42)      | Connecticut, 1935–1973           | Wilms' tumor cases | 19                     | 149             | Birth certificates            | At birth                  | Social class, birthplace, pregnancy history, parents' ages and birthplace, birth weight, length of gestation |
| (43)      | Columbus, Ohio area, 1950–1967   | Wilms' tumor cases | None                   | 62              | Birth certificates            | At birth                  | Age, sex, race, birth weight, parents' ages, birth order, county |
| (44)      | Columbus, Ohio area, 1950–1967   | Wilms' tumor cases | None                   | 62              | Birth certificates            | At birth                  | Age, sex, race, birth weight, parents' ages, birth order, county |
| (45)      | Philadelphia area, 1970–1983     | Wilms' tumor cases | 15                     | 88              | Random digit dialing          | 18 years old to 6 months before diagnosis | Age, race |

**Urinary system cancers**

| Reference | Study location and study period | Case group | Upper age limit, years | Number of cases | Source of exposure information | Time period of exposure | Potential confounders considered |
|-----------|---------------------------------|------------|------------------------|-----------------|-------------------------------|-------------------------|----------------------------------|
location, the range of occupations covered and the implications of a given job title for specific exposures might differ. For example, Peters et al. (35) focused on aircraft industry employment in their study of brain tumors due to the concentration of this industry in the Los Angeles area. Their findings could not be addressed in studies in Massachusetts (28), Baltimore (28), or Ohio (40) because of the rarity of such employment in those areas. If work conditions vary, for example, between the United States and China, then the exposure implications of a given job title (e.g., machinist, textile worker) could produce discrepant results.

The earliest eligibility dates for case diagnoses ranged from 1935 (42) to 1980 (32,34) with the end of eligibility ranging from 1967 (43,44) to 1986 (39) (Table 1). Exposures associated with a particular occupational title might be expected to differ over time as industrial processes and exposure standards change. In general, work environments have improved over time so that a failure to observe excess risk in more recent periods may not negate the causal implications of excess risks observed in earlier time periods.

The cancer type and vital status of cases (incident versus deceased) varied across the studies (Table 1). Variations in the composition of case groups could affect study results since the determinants of childhood cancer may be specific to the cancer type (43). If parental occupation influenced survival by affecting access to health care, for instance, then the studies of deceased cases might reach invalid conclusions regarding etiologic associations.

Case groups ranged in size from 43 brain tumor cases (24) to Sanders 6,920 cancer deaths (26) (Table 1). Because study group size is as important a determinant of the p-values as the magnitude of effect, a given odds ratio from a large study will attain significance more readily than that from a smaller study. The statistical significance of findings is therefore not emphasized in the interpretation of results.

Controls were usually derived from birth certificates or sampled from the general population (Table 1). Controls who were ill were included in three studies (24,27,28) in an attempt to minimize reporting bias among parents of children who had severe health problems. To adequately reflect the exposure distribution in the underlying population at risk, however, it must be assumed that exposure is unrelated to the controls' diseases and that those children with illnesses other than cancer come from the same base population.

Exposure was established based on occupation in birth certificates (9 studies), interviews (12 studies), medical records (1 study), death certificates (1 study), or questionnaires (1 study). Studies that rely on recorded data from birth certificates, medical records, or death certificates have the virtue of unbiased ascertainment but provide no control over the accuracy or level of detail of the information provided. Interviews provide an opportunity for more detailed discussion of specific exposures with some potential for respondent or interviewer bias, although it is not likely that parents' suspicions would lead to misreporting of occupation. Given the relative ease of obtaining occupational titles from birth certificates, it is unfortunate that none of the studies that selected controls from birth certificates and conducted personal interviews to ascertain exposure (28,41) addressed the comparability of exposure information from these two data sources. Relative to the true exposures of interest, both certificates and interview information are obviously imperfect to an unknown but probably substantial degree.

Studies that relied on birth certificates for exposure information could only consider exposures near the time of birth. Interview studies were able to examine exposures in the period preceding birth (generally 1 year) as well as the period preceding the child's diagnosis. In principle, different mechanisms of effect (i.e., a preconception genetic effect, in utero exposure, or postnatal exposure to the child) could be identified in the latter studies, but the job stability throughout the interval, especially for fathers, limits such analyses.

The potential confounders available for consideration largely reflect the mode of data acquisition (Table 1). Certificate-based studies only had access to demographic information, including parental ages, race, residence, and education, child's sex, and mother's pregnancy history. Interview studies generally obtained information on parental occupation as well as many other potential risk factors, so that other potential determinants of cancer risk could be examined as confounders. Given the paucity of information on etiologic factors in childhood cancer (43), it is difficult to argue that confounding occurred in studies with less extensive data on extraneous factors. Adjustments for potential confounders such as parents' ages, child's sex, race, and birth weight generally did not change the results markedly.

**Study Results**

Table 2 summarizes the results of studies of paternal exposures and total childhood cancer, including the initial report by Fabia and Thuy (22). Most studies have focused on exposures to hydrocarbons and other industrial chemicals. Two studies reported odds ratios of two or greater for mechanics (22,27), with contradictory results from Kwa and Fine (23). Odds ratios of 2 to 5 were observed by Hicks et al. (27) for aircraft workers and radiation-exposed military workers. Sporadic elevations in odds ratios were found for machinists, printers, and farmers, based on a single study with nonsupportive results reported in one or more investigations. None of the studies reporting results for hydrocarbons warranted inclusion based on the criteria defined earlier.

A noteworthy finding in Table 2 is the suggestive risk increases associated with occupations in which toxic exposures are not expected, such as men with an academic degree (25) and professionals, administrators, and clerical workers (26). These associations may reflect the increased incidence of childhood leukemias in the higher social classes (48), and serve as a reminder that occu-
Table 2. Results of studies of paternal occupation and total childhood cancer.

| Occupation                     | Number of exposed cases | Odds ratioa | Reference |
|--------------------------------|-------------------------|-------------|-----------|
| Mechanic                       |                         |             |           |
| Motor vehicle mechanic         | 28                      | 2.2b        | (22)      |
| Mechanic, gas station attendant| 35                      | 1.1         | (23)      |
| Aircraft mechanics             | 6                       | 2.3–infinity* | (27)    |
| Machinist                      |                         |             |           |
| Machinist, miner, lumberman    | 9                       | 0.5–1.8     | (24)      |
| Machine repairman              | 46c                     | 0.9         | (25)      |
| Radiation and military         |                         |             |           |
| Radiation-related              | 30                      | 1.5–2.0     | (27)      |
| Radiation-exposed military     | 13                      | 2.1–5.2*    | (27)      |
| Radar related                  | 21                      | 1.1–2.1     | (27)      |
| Armed forces                   | 157                     | 0.8         | (26)      |
| Electrical                     |                         |             |           |
| Electrician, plumber, carpenter| 12                      | 0.9–1.5     | (24)      |
| Electrical                     | 209                     | 1.0         | (26)      |
| Other industrial exposures     |                         |             |           |
| Printer                        | 15                      | 1.8         | (22)      |
| Petroleum industry             | 22                      | 0.7–1.6     | (24)      |
| Aircraft workers               | 13                      | 3.1–5.2*    | (27)      |
| Agriculture                    |                         |             |           |
| Farmers                        | 450b                    | 1.2*        | (25)      |
| Farmers                        | 274                     | 1.1         | (26)      |
| No industrial exposures        |                         |             |           |
| With academic degree           | 61b                     | 1.7         | (25)      |
| Professional, technical workers, artists | 687   | 1.4*        | (26)      |
| Administrators and managers    | 302                     | 1.7*        | (26)      |
| Clerical workers               | 376                     | 1.3*        | (26)      |
| Sales workers                  | 539                     | 1.3*        | (26)      |

a Range of odds ratios provided when multiple control groups were used.
b Number of exposed cases not provided; number of discordant pairs listed.
c p < 0.05.

Exposure to paints and pigments yielded the most consistently positive results, with five studies (22, 25,31,32,34) producing odds ratios of 1.5 or greater. Isolated findings implicate plastic and rubber, chlorinated solvents, petroleum products, food and drink manufacturing, and medical and social services.

Nervous system cancers, consisting primarily of brain tumors and neuroblastomas, were examined in a large number of studies (Table 4). The possibility of site-specificity of etiologic agents should be considered in reviewing these results, especially for neuroblastoma compared to brain and central nervous system cancers.

Motor vehicle-related occupations were found to be overrepresented among case fathers by Fabia and Thuy (22) and to a lesser extent by Wilkins and Koutras (40), but not by four other investigators (23,25,37,39). An odds ratio of 4.4 for machine repairmen (25) was not replicated (23,28,39,40). Risk elevations were again noted for painters, with strongly positive results from two studies (ORs = 2.6, 7.0) (25,35) and null results from two others (39,40).

Exposures associated with the chemical and petroleum industries produced reasonably consistent indications of a positive association, with odds ratios of 1.5 or greater in three studies (35,39,41) and of 3.0 or greater in two studies (35,39). Hydrocarbon exposures in the aggregate were only associated with nervous system cancers in the study of neuroblastoma (37) and not in the three studies of central nervous system cancers (26,28,41). Metal-related work was associated with brain cancer, but in only one study (40).

Three studies (37,40,41) found elevated risks associated with assorted electrical occupations. Both Hicks et al. (27) and Nasca et al. (41) found ionizing radiation to be associated with nervous system cancers, with odds ratios around two. Isolated reports implicate metal-related occupations, farming, construction, aircraft industry, printing, and graphic arts in brain cancer risk, though the associations were either not examined or not confirmed in other studies. The three studies that included data on paper and pulp mill workers (23,39,41) all noted increased odds ratios, ranging from 1.6 to 4.0.

Urinary system cancers were the focus of several studies (42–45) (Table 5). Hydrocarbon exposures were implicated by Kantor et al. (42) and Kwa and Fine (23), but not confirmed in other studies (26,41,42). Similarly, lead was rather strongly linked to Wilms' tumor in one study (42) but not others (43,44). Radiation exposure was associated with Wilms' tumor risk in two studies (27,45), each reporting odds ratios of two or greater. Boron has also been identified as a risk factor in two studies (43,45). The plausibility of environmental contaminants acting on the kidney encourages further evaluation of the postulated associations.

Maternal exposures to occupational hazards (Table 6) were addressed in few of the studies, primarily because of the rarity with which mothers had worked in potentially hazardous workplaces. Hemminki et al. (25) found total cancer risk to be associated with work as a pharmacists, farmer, baker, or in the food industry.

pational titles may be associated with childhood cancer through mechanisms other than environmental exposures.

Studies of paternal occupation in relation to childhood leukemias and lymphomas are summarized in Table 3. Motor vehicle related occupations (mechanics, drivers) were associated with elevated risks in some studies (22,28,32) but not in others (23,31). Machinists and factory workers also showed several associations of 2-fold or greater (22,28,32,34), but the diversity of jobs makes it difficult to evaluate the consistency of the data. Hydrocarbon exposures were strongly related to leukemia in the study by Vianna et al. (29) of cases age 1 year or less. Sanders et al. (26) and Van Steensel-Moll et al. (31) failed to confirm that finding with cases covering a broader age range.
Table 3. Results of studies of paternal occupation and childhood leukemias and lymphomas.

| Occupation                                      | Cancer site              | Number of exposed cases | Odds ratio* | Reference |
|-------------------------------------------------|--------------------------|-------------------------|-------------|-----------|
| Motor vehicle related                           |                          |                         |             |           |
| Motor vehicle mechanic, service station attendant| Leukemia/lymphoma        | 16                      | 2.09        | (22)      |
| Mechanic, gas station attendant                 | Leukemia/lymphoma        | 21                      | 1.1         | (23)      |
| Motor vehicle driver                            | Leukemia/lymphoma        | 28                      | 1.0         | (23)      |
| Motor vehicle driver                            | Leukemia                 | 96b                     | 1.5         | (25)      |
| Motor vehicle related                           | Leukemia                 | 6                       | 0.8, infinity* | (28)  |
| Auto mechanic, machinist, gas station attendant, miner | Acute lymphocytic leukemia | 18                     | 0.8         | (31)      |
| Transportation                                  | Acute leukemia            | 22b                     | 1.4         | (32)      |
| Transportation equipment                        | Acute leukemia            | 21b                     | 2.5         | (32)      |
| Transportation equipment operator               | Leukemia                 | 24                      | 1.2         | (33)      |
| Machinist and factory worker                   |                          |                         |             |           |
| Machinist, miner, lumberman                     | Leukemia/lymphoma        | 23                      | 2.5         | (22)      |
| Machinist                                      | Leukemia/lymphoma        | 49                      | 1.3         | (23)      |
| Machine repairmen                              | Leukemia                 | 15b                     | 0.3         | (25)      |
| Factory worker, machinist, and related occupations | Leukemia               | 11                      | 0.8,2.5     | (28)      |
| Operators, fabricators, laborers               | Leukemia                 | 57                      | 1.1         | (30)      |
| Manual and mechanical skills                   | Acute lymphocytic leukemia | 188                  | 1.0         | (31)      |
| Machinery                                      | Acute leukemia            | 20b                     | 3.0         | (22)      |
| Aircraft manufacturing                          | Acute leukemia            | 17b                     | 1.8         | (22)      |
| Blacksmiths, toolmakers, etc.                   | Leukemia                 | 50                      | 0.9         | (33)      |
| Nonauto mechanic                               | Acute nonlymphocytic leukemia | 14                 | 3.5         | (34)      |
| Aggregated hydrocarbon                          |                          |                         |             |           |
| Hydrocarbon related                            | Leukemia                 | 202,416                 | 0.9,1.0     | (26)      |
| Hydrocarbon related                            | Leukemia                 | 7.10b                   | 1.0,2.5     | (28)      |
| Hydrocarbon, high                              | Acute leukemia            | 24,28b                  | 2.4,2.5     | (29)      |
| Hydrocarbon, low                               | Acute leukemia            | 19,22b                  | 1.3,3.8     | (29)      |
| Hydrocarbon related                            | Acute lymphocytic leukemia | 37                   | 1.0         | (31)      |
| Paints and pigments                            |                          |                         |             |           |
| Painter, dyer, cleaner                         | Leukemia/lymphoma        | 5                       | 1.7         | (22)      |
| Painter                                        | Leukemia/lymphoma        | 7                       | 0.9         | (23)      |
| Painter                                        | Leukemia                 | 12b                     | 1.5         | (25)      |
| Painter, cleaner, dyer                         | Acute lymphocytic leukemia | 8                   | 1.6         | (31)      |
| Pigments (dyes) exposure                       | Acute lymphocytic leukemia | 25                | 1.6         | (31)      |
| Spray paint                                    | Acute leukemia            | 26b                     | 2.2         | (29)      |
| Dyes, pigments                                 | Acute leukemia            | 8b                      | 3.0         | (29)      |
| Painter                                        | Acute nonlymphocytic leukemia | 7                    | 7.0         | (34)      |
| Food related                                   |                          |                         |             |           |
| Baker, cook, restaurant worker                 | Leukemia/lymphoma        | 12                      | 1.4         | (23)      |
| Food preparation                               | Leukemia                 | 3b                      | 0.5         | (30)      |
| Foods and drink manufacturing                  | Acute leukemia            | 13b                     | 2.2         | (22)      |
| Other chemicals                                |                          |                         |             |           |
| Tar or asphalt exposure                        | Acute lymphocytic leukemia | 26                 | 1.1         | (31)      |
| Petroleum chemicals manufacturing              | Acute leukemia            | 16b                     | 1.0         | (32)      |
| Petroleum products                             | Acute nonlymphocytic leukemia | NA               | 2.8         | (44)      |
| Plastic or rubber exposure                     | Acute lymphocytic leukemia | 25                 | 2.0         | (31)      |
| Chemical, rubber, and plastics workers         | Leukemia                 | 12                      | 1.1         | (23)      |
| Plastics                                       | Acute nonlymphocytic leukemia | NA             | 1.5         | (34)      |
| Chlorinated solvents                           | Acute leukemia            | 13b                     | 2.2         | (32)      |
| Solvents                                       | Acute nonlymphocytic leukemia | NA               | 2.1*        | (34)      |
| Other occupations                              |                          |                         |             |           |
| Medical and social services                    | Acute lymphocytic leukemia | 18                  | 2.8         | (31)      |
| Medical and public health workers              | Leukemia                 | 5                       | 0.6         | (33)      |

*Range of odds ratios provided when multiple control groups were used.

*Number of exposed cases not provided; number of discordant pairs listed.

*NA, not available.

*p < 0.05.
Table 4. Results of studies of paternal occupation and childhood nervous system cancers.

| Occupation                              | Cancer site                          | Number of exposed cases | Odds ratio* | Reference |
|----------------------------------------|--------------------------------------|-------------------------|-------------|-----------|
| Motor vehicle related                  |                                      |                         |             |           |
| Motor vehicle mechanic, service station attendant | Nervous system                      | 10                      | 2.8*        | (23)      |
| Mechanic, gas station attendant        | Nervous system                       | 6                       | 1.0         | (23)      |
| Motor vehicle driver                   | Nervous system                       | 5                       | 0.6         | (23)      |
| Motor vehicle driver                   | Brain                                | 84                     | 0.9         | (25)      |
| Transportation, utilities, communication | Neuroblastoma                        | 12                      | 0.9         | (27)      |
| Motor vehicle mechanic, service station attendant | Nervous system                      | NA                      | 0.7         | (39)      |
| Motor freight and transportation       | Brain                                | 37                      | 1.6         | (40)      |
| Machinist and factory worker           |                                      |                         |             |           |
| Machinist                              | Nervous system                       | 9                       | 0.7         | (23)      |
| Machine repairman                      | Brain                                | 14b                     | 4.4*        | (25)      |
| Factory worker, machinist, and related occupations | Brain                                | 16                      | 0.7,2.5     | (23)      |
| Factory worker, machinist, and steelworker | Nervous system                      | NA                      | 1.0         | (39)      |
| Machine trades occupations             | Brain                                | 66                      | 1.2         | (40)      |
| Paint                                  |                                      |                         |             |           |
| Painter                                | Brain                                | 14b                     | 2.6         | (23)      |
| Paint exposure                         | Brain                                | 7                       | 7.0*        | (25)      |
| Painter                                | Nervous system                       | NA                      | 1.0         | (39)      |
| Painting, plastering, etc.             | Brain                                | 7                       | 1.2         | (40)      |
| Chemicals                              |                                      |                         |             |           |
| Chemical solvent exposure              | Brain                                | 20                      | 2.8*        | (23)      |
| Chemical industry                      | Nervous system                       | 12                      | 1.4         | (23)      |
| Chemical workers                       | Nervous system                       | 6                       | 0.8         | (23)      |
| Chemical and petroleum refinery worker | Nervous system                       | 9                       | 3.0*        | (23)      |
| Chemical and drug salesman             | Nervous system                       | 5                       | 10.0*       | (23)      |
| Chemical industry                      | CNS tumors                           | 10                      | 1.5         | (41)      |
| Petroleum industry                     |                                      |                         |             |           |
| Oil and gas extraction                 | Neuroblastoma                        | 8                       | 1.3         | (37)      |
| Petroleum refinery worker              | Nervous system                       | 6                       | 2.0         | (39)      |
| Petroleum industry                     | CNS tumors                           | 9                       | 3.1         | (41)      |
| Aggregated hydrocarbon                 |                                      |                         |             |           |
| Hydrocarbon related                    | Brain                                | 419                     | 0.9         | (23)      |
| Hydrocarbon related                    | Brain                                | 11                      | 0.5,2.3     | (23)      |
| Aromatic hydrocarbons, nonionizing radiation | Neuroblastoma                    | 5                       | 1.8         | (37)      |
| Aromatic and aliphatic hydrocarbons   | Neuroblastoma                        | 10                      | 3.2*        | (37)      |
| Hydrocarbon related, narrow definition | CNS tumors                           | 18                      | 1.3         | (41)      |
| Hydrocarbon related, broad definition  | CNS tumors                           | 38                      | 1.4         | (41)      |
| Electrical                             |                                      |                         |             |           |
| Electronics workers                    | Neuroblastoma                        | 6                       | 11.8*       | (37)      |
| Electrical assembling, installing, and repairing | Brain                                | 19                      | 2.7*        | (40)      |
| Electromagnetic fields, narrow definition | CNS tumors                           | 15                      | 1.7         | (41)      |
| Electromagnetic fields, broad definition | CNS tumors                           | 19                      | 1.6         | (41)      |
| Ionizing radiation                     |                                      |                         |             |           |
| Industrial, less exposure              | Nervous system                       | 10                      | 1.0–1.1     | (27)      |
| Occupation, less exposure              | Nervous system                       | 7                       | 1.8–2.1     | (27)      |
| Industrial, more exposure              | CNS tumors                           | 28                      | 2.9*        | (41)      |
| Industrial, less exposure              | CNS tumors                           | 61                      | 1.7*        | (41)      |
| Occupation, more exposure              | CNS tumors                           | 19                      | 1.0         | (41)      |
| Occupation, less exposure              | CNS tumors                           | 31                      | 1.1         | (41)      |
| Metals                                 |                                      |                         |             |           |
| Metal processors and producers         | Brain                                | 62                      | 1.9*        | (40)      |
| Welders, cutters                       | Brain                                | 11                      | 2.7         | (40)      |
| Metal working occupations              | Brain                                | 14                      | 1.6         | (40)      |

(continued)
### Table 4. Continued.

| Occupation                        | Cancer site         | Number of exposed cases | Odds ratio<sup>a</sup> | Reference |
|-----------------------------------|---------------------|-------------------------|-------------------------|-----------|
| **Agriculture**                   |                     |                         |                         |           |
| Farmer                            | Nervous system      | 6                       | 0.6                     | (22)      |
| Farmer                            | Brain               | 107<sup>b</sup>         | 1.2                     | (25)      |
| Agriculture                       | Neuroblastoma       | 6                       | 0.6                     | (37)      |
| Farming and agricultural occupations | Brain             | 30                      | 2.0<sup>b</sup>         | (40)      |
| **Construction**                  |                     |                         |                         |           |
| Construction                      | Neuroblastoma       | 17                      | 0.9                     | (37)      |
| Construction industry             | Brain               | 47                      | 2.3*                    | (40)      |
| Construction occupations          | Brain               | 26                      | 2.0*                    | (40)      |
| Carpenters                        | Brain               | 14                      | 1.9                     | (40)      |
| **Paper and pulp mill**           |                     |                         |                         |           |
| Paper and pulp mill               | Nervous system      | 6                       | 2.8*                    | (23)      |
| Paper and pulp mill worker        | Nervous system      | NA                      | 4.0                     | (39)      |
| Pulp and paper industry           | CNS tumors          | 8                       | 1.6                     | (41)      |
| **Aerospace and aircraft industries** |                 |                         |                         |           |
| Aircraft industry                 | Brain               | 12                      | Infinity*<sup>c</sup>   | (35)      |
| Aerospace occupation              | Brain               | 7                       | 1.1                     | (38)      |
| Aircraft industry worker          | Nervous system      | NA                      | 1.0                     | (39)      |
| **Other occupations**             |                     |                         |                         |           |
| Printing workers                  | Nervous system      | 9                       | 4.5*                    | (39)      |
| Graphic arts workers              | Nervous system      | 5                       | 21.9*                   | (39)      |
| Glass, clay, stone industry       | Brain               | 12                      | 1.5                     | (40)      |

<sup>a</sup> Range of odds ratios provided when multiple control groups were used.

<sup>b</sup> Number of exposed cases not provided; number of discordant pairs listed.

<sup>c</sup> NA, not available.

*<sup>p</sup> < 0.05.

### Table 5. Results of studies of paternal occupation and childhood urinary system cancers.

| Occupation                          | Cancer site         | Number of exposed cases | Odds ratio<sup>a</sup> | Reference |
|-------------------------------------|---------------------|-------------------------|-------------------------|-----------|
| **Hydrocarbon related**             |                     |                         |                         |           |
| Motor vehicle mechanic              | Wilms' tumor        | 6                       | 6.2                     | (42)      |
| Machinist                           | Wilms' tumor        | 5                       | 1.7                     | (42)      |
| Mechanic, gas station attendant, machinist | Urinary tract     | 10                      | 2.6*                    | (23)      |
| Machinist                           | Wilms' tumor        | 9                       | 3.2                     | (45)      |
| Hydrocarbon related                 | Kidney              | 111                     | 1.2                     | (28)      |
| Soot exposure                       | Wilms' tumor        | 16                      | 0.8                     | (43)      |
| Hydrocarbon related                 | Wilms' tumor        | 10                      | 1.4                     | (44)      |
| Benzo(a)pyrene exposure             | Wilms' tumor        | 15                      | 0.8                     | (43)      |
| **Lead exposure**                   |                     |                         |                         |           |
| Lead related                        | Wilms' tumor        | 22                      | 3.7*                    | (42)      |
| Lead exposure                       | Wilms' tumor        | 18                      | 1.1                     | (43)      |
| Lead related                        | Wilms' tumor        | 11                      | 1.3                     | (44)      |
| **Radiation related**               |                     |                         |                         |           |
| Radiation-related industry          | Wilms' tumor        | 18<sup>b</sup>          | 2.5*–2.6*               | (27)      |
| Radiation                           | Wilms' tumor        | 18<sup>b</sup>          | 2.0                     | (45)      |
| Radium                              | Wilms (nongenetic)  | 5<sup>b</sup>           | 4.0                     | (45)      |
| **Other occupational exposures**    |                     |                         |                         |           |
| Trichloroethylene exposure          | Wilms' tumor        | 10                      | 1.5                     | (43)      |
| Boron exposure                      | Wilms' tumor        | 7<sup>b</sup>           | 3.5*                    | (43)      |
| Boron                               | Wilms (genetic)     | 5<sup>b</sup>           | Infinity                | (45)      |
| Dichloroethyl ether                 | Wilms (genetic)     | 5<sup>b</sup>           | 4.0                     | (45)      |
| Nitroparaffins                      | Wilms (genetic)     | 6<sup>b</sup>           | 5.0                     | (45)      |

<sup>a</sup> Range of odds ratios provided when multiple control groups were used.

<sup>b</sup> Number of exposed cases not provided; number of discordant pairs listed.

*<sup>p</sup> < 0.05.
Table 6. Results of studies of maternal occupation and childhood cancer.

| Occupation                                      | Number of exposed cases | Odds ratio | Reference |
|------------------------------------------------|-------------------------|------------|-----------|
| Total cancers                                   |                         |            |           |
| Pharmacist                                      | 12                      | 3.2*       | (25)      |
| Agriculture, gardening, forestry                | 29                      | 1.7        | (25)      |
| Food industry                                   | 37                      | 2.1*       | (25)      |
| Baker                                           | 20                      | 2.4        | (25)      |
| Leukemia                                        |                         |            |           |
| Pharmacist                                      | 5*                      | 2.6        | (25)      |
| Pharmacist                                      | NA                      | 19.7*      | (33)      |
| Medical and social services                     | 21                      | 1.0        | (31)      |
| Physicians                                      | NA                      | 5.7*       | (33)      |
| Manual and mechanical skills                    | 15                      | 2.0        | (31)      |
| Blacksmiths, toolmakers, etc.                   | 32                      | 1.1        | (33)      |
| Metal refining and processing                   | 8                       | 2.6        | (33)      |
| Lead                                            | 5                       | 2.3        | (33)      |
| Metal dusts                                     | NA                      | 3.0        | (34)      |
| Textile industry                                | 8                       | 4.2*       | (31)      |
| Textile workers and tailors                     | 27                      | 0.7        | (33)      |
| Chemical exposure                               | 25                      | 2.4*       | (31)      |
| Chemical processors                             | 25                      | 3.3*       | (33)      |
| Hydrocarbon related                             | 7                       | 2.5        | (31)      |
| Benzene                                         | 24                      | 2.0        | (33)      |
| Gasoline                                        | 38                      | 1.6        | (33)      |
| Toluene                                         | 20                      | 1.5        | (33)      |
| Kerosene                                        | 16                      | 1.6        | (33)      |
| Diesel oil                                      | 16                      | 1.6        | (33)      |
| Pigment (dyes) exposure                         | 22                      | 1.8        | (31)      |
| Paints and pigments                             | Not stated              | 1.5        | (34)      |
| Personal service industries                     | 12                      | 2.7*       | (33)      |
| Service workers                                 | 34                      | 1.4        | (33)      |
| Domestics, hotel, and catering                  | 24                      | 2.8*       | (31)      |
| Agriculture and forestry                        | 12                      | 2.3        | (33)      |
| Pesticides                                      | 12                      | 3.5        | (33)      |
| Pesticides                                      | NA                      | 6.0*       | (34)      |
| Brain cancer                                    |                         |            |           |
| Chemicals on skin                               | 10                      | 3.3        | (33)      |
| Inhaled chemicals or fumes                      | 13                      | 3.0        | (33)      |
| Baker                                           | 9*                      | 1.6        | (25)      |
| Wore protective clothing or equipment (exposure proxy) | 15*                     | 4.0*       | (24)      |
| Wilms’ tumor                                    |                         |            |           |
| Aromatic amino compounds                        | 5*                      | Infinity   | (45)      |

* Number of exposed cases not provided; number of discordant pairs listed.

NA, not available.

*p < 0.05.

Occupations found more frequently among mothers of children with leukemia included a wide variety of chemical exposures. Notably strong or replicated associations were found for work as a pharmacist (25), in metal manufacturing or processing (33,34), textiles (31), pigments (31,34), or unspecified chemicals (31,33). Studies of maternal occupation and brain cancer (33,34) produced strong positive associations with chemical hazards in general (ORs of 3.0–4.0). Unfortunately, there is very limited opportunity to have these results corroborated given the few studies of maternal occupation.

**Discussion**

In spite of a large number of studies, no specific parental occupational exposure has been established as a cause of childhood cancer. However, several paternal occupations have been found to be associated with childhood leukemias and nervous system tumors and maternal occupations with several cancers based on the magnitude of odds ratios and replication in two or more studies. The most promising leads for further study are paternal paint exposure and to a lesser extent paternal hydrocarbon exposure in relation to both childhood leukemias and brain cancer. Paternal work with ionizing radiation and work in the petroleum, chemical, electrical, and paper industries should be further evaluated in relation to childhood brain cancer. Maternal exposures have received relatively little attention, but the few studies have yielded strongly suggestive results implicating a variety of occupational chemicals in leukemia and brain cancer.
There was a tendency for specific studies to produce many elevated or many null odds ratios, with no clear methodological basis given their methodological similarity (Table 1). The most parsimonious explanation for generating an array of positive associations with industrial exposures would be having selected an unsuitable control group. False negative results are also readily accounted for by poor exposure assessment or overly broad groupings of disease.

Positive results were more common in studies of nervous system cancers (Table 4) than studies of leukemia (Table 3) or urinary system cancer (Table 5), either reflecting more causal relationships or superior study methods. Again, there is no obvious pattern based on the study attributes summarized in Table 1.

There are several important methodological limitations pervasive in this literature that would tend to obscure associations. Exposure classification is the most critical. The exposures of ultimate interest are specific physical or chemical agents in the workplace that reach the parent. The ability of the surrogates used in these studies (typically a job title alone) to accurately identify exposed and unexposed individuals is highly questionable. The associations are virtually all between occupation and childhood cancer, not actually between an occupational exposure and childhood cancer. Job titles may not accurately identify exposures due to errors in reporting, but especially due to the inherent variability in activities and environments associated with any given job title. Different industrial processes, variable use of protective equipment, and differing activities within a job title contribute to this heterogeneity in exposure.

Many studies have chosen to address exposure aggregations such as hydrocarbons or chemical industry employment. If only a subset of those agents actually affected childhood cancer risk, then the aggregation itself constitutes an additional form of misclassification.

The direction of bias from these sources of error is predictable since the same methods of imputing exposure were applied to cases and controls: the misclassification is nondifferential with respect to disease status, resulting in a bias toward the null (no association) (49). Superimposed on any underlying etiologic associations between chemical or physical agents and childhood cancer is this dilution from exposure misclassification.

Exposure classification will remain the major challenge in this research area because the rarity of childhood cancer precludes conducting true prospective studies in which exposures of parents are carefully monitored from before conception to the time of diagnosis. The challenge of retrospective exposure assignment sometimes occurring years after the time period of interest must be addressed. The limitations of occupational data from death certificates is well known (50, 51), but at least some of the problems of using job titles from death certificates as exposure indicators for the study of adult cancer or other chronic diseases are not as great of a concern in using job titles from birth certificates as exposure indicators for the study of childhood cancer. The uncertainty over how recently the job was held or whether the job was held for a sufficiently lengthy period to affect disease are less problematic for studies of childhood cancer. Nonetheless, job titles from interviews with the parents are likely to be superior to job titles reported on birth certificates (52, 53). In an interview, there is an opportunity to probe incomplete answers and ask about specific work activities.

The application of an exposure linkage system to aggregate occupations into exposure groups (54) as implemented by Wilkins and Sinks (44), Buckley et al. (34), and Bunin et al. (45) constitutes an improvement over purely subjective aggregations of jobs. The original motivation for developing such linkage systems was principally to aggregate diverse jobs with common exposures (54), a particular problem in studies of limited size. Inaccuracies in assigning exposures based on job titles are not avoided (55), but investigators could at least generate comparable results.

A more complete solution is to conduct detailed interviews to ascertain exposure histories, as illustrated by Guerin et al. (56). In the investigation of occupational cancers developed by Siemiatycki et al. (57), a preliminary structured interview regarding occupational exposures is followed by a semistructured interview by an industrial hygienist. This provides an opportunity for querying important aspects of exposure not identifiable through job title such as industrial processes, environmental controls, specific work locations, and responsibilities. None of the studies conducted to date have been nearly that ambitious, although an investigation devoting considerable resources to exposure assessment would be both justified by the existing literature and feasible for studies of parental occupation and childhood cancer.

Other methodological considerations are also worth noting. The constitution of the case groups varied across studies and could account for inconsistency in the results since childhood cancers are likely to have etiologic factors that vary by age at diagnosis and disease category. The isolation of very young leukemia cases by Vianna et al. (29) may have affected their results relative to other studies, either because etiologic factors are distinctive for early cases or because the recall of occupation is improved with a shorter time period of recall (from pregnancy to diagnosis). The known causal influences on childhood cancer are so limited (48) that the suggestion of etiologic specificity is based primarily on an analogy with the specificity often found for adult cancers. Until more is learned about the etiology of childhood cancers, it is preferable to conduct studies in which homogeneous subgroups of cases can be analyzed.

The precision of risk estimates remains an important concern. The rarity of childhood cancer makes it difficult for individual investigators to accumulate a sufficiently large case group to form subgroups defined by age or diagnosis with precise estimates of effect. One possible solution to this problems is for collaborative investigations to be initiated to enable inclusion of adequate numbers of cases (34). Alternatively, investigators should group both exposure and disease in a manner
allowing for aggregation across studies, for example by applying a universal occupational coding system and using a standard cancer classification system. Larger study groups will not eliminate the concerns with the accuracy of exposure definition, but could diminish the impact of random variation on the observed results and allow examination of more homogeneous case groups.

In spite of these limitations and the inconclusive results of past studies, continued evaluation of parental occupation and childhood cancer is clearly warranted. Childhood cancer exerts a major toll in years of life lost and in the psychological burden borne by the families of victims and by cancer survivors. While acknowledging the substantial methodological challenges in advancing our understanding, more sophisticated approaches to exposure assessment that have been applied to the etiology of adult cancers would be applicable to the study of childhood cancer. Future evaluations of the reproductive toxicity of environmental agents need to include carcinogenicity in the offspring, with particular emphasis on improved exposure assessment.

The authors acknowledge the contributions of Linda Morse and Eileen Nobles in preparation of the original manuscript and Sioban Harlow, Dana Loomis, Julie Marshall, Dennis Waite, and John Wilkins for their constructive reviews.

REFERENCES

1. Barlow, S. M., and Sullivan, F. M. Reproductive hazards of industrial chemicals. An evaluation of animal and human data. Academic Press, London, 1982.
2. Arundel, S. E., and Kinney-Wilson, L. M. Parental occupations and cancer: A review of the literature. J. Epidemiol. Comm. Health 40: 30–36 (1986).
3. Herbst, A. L., Uifelder, H., and Poskanzer, D. C. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N. Engl. J. Med. 294: 878–881 (1971).
4. Committee on the Biological Effects of Ionizing Radiations. The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980. National Academy Press, Washington, DC, 1980.
5. MacMahon, B. Prenatal x-ray exposure and twins. N. Engl. J. Med. 312: 575–577 (1985).
6. Office of Technology Assessment. Reproductive Health Hazards in the Workplace. U.S. Government Printing Office, Washington, DC, 1985.
7. Whorton, D., Krauss, R. M., Marshall, S., and Milby, T. H. Infertility in male pesticide workers. Lancet ii: 1259–1261 (1977).
8. Cohen, E. N., Brown, B. W., Jr., Bruce, D. L., Cascorbi, H. F., Corbett, T. H., Jones, T. W., and White, C. E. A survey of anesthetic health hazards among dentists. J. Am. Dent. Assoc. 90: 1291–1296 (1975).
9. Infante, P. F., Wagoner, J. K., McMichael, A. J., Waxweiler, R. J., and Falck, H. Genetic risks of vinyl chloride. Lancet i: 734–735 (1976).
10. Tanabeum, T. N., and Goldberg, R. J. Exposure to anesthetic gases and reproductive outcome. A review of the epidemiologic literature. J. Occup. Med. 27: 659–668 (1985).
11. Vessey, M. P., and Nunn, J. F. Occupational hazards of anesthe sia. Br. Med. J. 281: 696–698 (1980).
12. Selevan, S. G., Lindbohm, M.-L., Hornung, R. W., and Hemminki, K. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. N. Engl. J. Med. 318: 1173–1178 (1986).
13. Strobino, B. R., Kline, J., and Stein, Z. Chemical and physical exposures of parents: effects on human reproduction and offspring. Early Hum. Dev. 1: 371–399 (1978).
14. Kallen, B. Epidemiology of Human Reproduction. CRC Press, Inc., Boca Raton, FL, 1988.
15. Tomatis, L., Mohr, U., and Davis, W., Eds. Transplacental Carcinogenesis. International Agency for Research on Cancer, Lyon, France, 1973.
16. Knikshkow, B., and Baker, E. Transmission of occupational disease to family members. Am. J. Ind. Med. 9: 545–550 (1966).
17. Miller, R. W. Prenatal origins of cancer in man: epidemiological evidence. In: Transplacental Carcinogenesis (L. Tomatis, U. Mohr, and W. Davis., Eds.), International Agency for Research on Cancer, Lyon, France, 1973, pp. 1750–1780.
18. Fox, B. W., and Fox, M. Biochemical aspects of the actions of drugs on spermatogenesis. Pharmacol. Rev. 19: 21–57 (1967).
19. Trasler, J. M., Hales, B. F., and Robaire, B. Paternal cyclophosphamide treatment of rats causes fetal loss and malformations without affecting male fertility. Nature 316: 144–146 (1985).
20. Joffe, J. M., and Szyka, L. F. Paternal drug exposure: effects on reproduction and progeny. Semin. Perinatal 6: 114–124 (1982).
21. Tomatis, L., Cabral, J. R. P., Likhachev, A. J., and Ponomarkov, V. Increased cancer incidence in the progeny of male rats exposed to ethylnitrosourea before mating. Int. J. Cancer 28: 475–478 (1981).
22. Fabia, J., and Thuy, T. D. Occupation of father at time of birth of children dying of malignant disease. Br. J. Prev. Soc. Med. 29: 98–100 (1974).
23. Kwa, S.-L., and Pine, L. J. The association between parental occupation and childhood malignancy. J. Occup. Med. 22: 792–794 (1980).
24. Zack, M., Cannon, S., Loyd, D., Heath, C. W., Jr., Falletta, J. M., Jones, B., Housworth, J., and Crowley, S. Cancer in children of parents exposed to hydrocarbon-related industries and occupations. Am. J. Epidemiol. 111: 329–336 (1980).
25. Hemminki, K., Saloniemi, I., Salonen, T., Partanen, T., and Vainio, H. Childhood cancer and parental occupation in Finland. J. Epidemiol. Comm. Health 35: 11–15 (1981).
26. Sanders, B. M., White, G. C., and Draper, G. J. Occupations of fathers of children dying from neoplasms. J. Epidemiol. Comm. Health 35: 245–250 (1980).
27. Hicks, N., Zack, M., Caldwell, G. G., Fernbach, D. J., and Falletta, J. M. Childhood cancer and occupational radiation exposure in parents. Cancer 53: 1637–1643 (1984).
28. Gold, E. B., Diener, M. D., and Szko, M. Parental occupations and cancer in children. A case-control study and review of the methodologic issues. J. Occup. Med. 24: 578–584 (1982).
29. Vianna, N. J., Kovasznay, B., Polan, A., and Ju, C. Infant leukemia and paternal exposure to motor vehicle exhaust fumes. J. Occup. Med. 26: 679–682 (1984).
30. Shaw, G., Lavey, R., Jackson, R. and Austin, D. Association of childhood leukemia with parental age, birth order, and paternal occupation. Am. J. Epidemiol. 119: 788–796 (1984).
31. Van Steensel-Moll, H. A., Valkenburg, H. A., and Van Zanen, G. E. Childhood leukemia and parental occupation. A register-based case-control study. Am. J. Epidemiol. 121: 216–224 (1985).
32. Lowengart, R. A., Peters, J. M., Cicconi, C., Buckley, J., Bernstein, L., Preston-Martin, S., and Permpoparth, E. Childhood leukemia and parents' occupational and home exposures. J. Natl. Cancer Inst. 79: 39–46 (1987).
33. Shu, X. O., Gao, Y. T., Brinton, L. A., Linet, M. S., Tu, J. T., Zheng, W., and Fraumeni, J. F., Jr. A population-based case-control study of childhood leukemia in Shanghai. Cancer 62: 635–644 (1988).
34. Buckley, J. D., Robison, L. L., Swotinsky, R., Garabrant, D. H., LeBeau, M., Manchester, P., Neubit, M. E., Odom, L., Peters, J. M., Woods, W. G., and Hammond, G. D. Occupational exposures of parents of children with acute nonlymphocytic leukemia: a report from the Childrens Cancer Study Group. Cancer Res. 49: 4030–4037 (1989).
35. Peters, J. M., Preston-Martin, S., and Yu, M. C. Brain tumors in children and occupational exposure of parents. Science 213: 235–237 (1981).
36. Preston-Martin, S., Yu, M. C., Benton, B., and Henderson, B. E. Nitrosourea compounds and childhood brain tumors: a case-control study. Cancer Res. 42: 5240–5246 (1982).
37. Spitz, M. R., and Johnson, C. C. Neuroblastoma and paternal occupation. A case-control analysis. Am. J. Epidemiol. 121: 924–929 (1985).
38. Olshan, A. F., Breslow, N. E., Daling, J. R., Weiss, N. S., and Leviton, A. Childhood brain tumors and paternal occupation in the aerospace industry. J. Natl. Cancer Inst. 77: 17–19 (1986).
39. Johnson, C. C., Annegers, J. F., Frankowski, R. F., Spitz, M. R., and Buffler, P. A. Childhood nervous system tumors—an evaluation of the association of paternal occupational exposure to hydrocarbons. Am. J. Epidemiol. 126: 605–613 (1987).
40. Wilkins, J. R., III, and Koutras, R. A. Paternal occupation and brain cancer in offspring: a mortality-based case-control study. Am. J. Ind. Med. 14: 299–318 (1988).
41. Nasca, P. C., Baptiste, M. S., MacCubbin, P. A., Metzger, B. B., Carlton, K., Greenwald, P., Armbrustmacher, V. W., Earle, K. M., and Waldman, J. An epidemiologic case-control study of central nervous system tumors in children and parental occupational exposures. Am. J. Epidemiol. 128: 1256–1265 (1988).
42. Kantor, A. F., Curnen, M. G. M., Meigs, J. W., and Flannery, J. T. Occupation of fathers of patients with Wilms's tumour. J. Epidemiol. Comm. Health 33: 253–256 (1979).
43. Wilkins, J. R. III, and Sinks, T. H., Jr. Occupational exposures among fathers of children with Wilms' tumor. J. Occup. Med. 26: 427–435 (1984).
44. Wilkins, J. R. III, and Sinks T. H., Jr. Paternal occupation and Wilms' tumour in offspring. J. Epidemiol. Comm. Health 38: 7–11 (1984).
45. Bunin, G. R., Nass, C. C., Kramer, S., and Meadows, A. T. Parental occupation and Wilms' tumor: results of a case-control study. Cancer Res. 49: 725–729 (1989).
46. Savitz, D. A. Childhood cancer. In: Reproductive Problems in the Workplace. Occupational Medicine: State of the Art Reviews, Vol. 1 (Z. A. Stein and M. C. Hatch, Eds.). Hanley and Belfus, Philadelphia, PA, 1986, pp. 415–429.
47. Miettinen, O. S., and Wang, J-D. An alternative to the proportionate mortality ratio. Am. J. Epidemiol. 114: 144–148 (1981).
48. Greenberg, R. S., and Schuster, J. L., Jr. Epidemiology of cancer in children. Epidemiol. Rev. 7: 22–48 (1985).
49. Copeland, K. T., Checkoway, H., McMichael, A. J., and Holbrook, R. H. Bias due to misclassification in the estimation of relative risk. Am. J. Epidemiol. 105: 488–498 (1977).
50. Steenland, K., and Beaumont, J. The accuracy of occupation and industry data on death certificates. J. Occup. Med. 26: 288–296 (1984).
51. Schade, W. J., and Swanson, G. M. Comparison of death certificate occupation and industry data with lifetime occupational histories obtained by interview: variations in the accuracy of death certificate entries. Am. J. Ind. Med. 14: 121–136 (1988).
52. Baumgarten, M., Siemiatycki, J., and Gibbs, G. W. Validity of work histories obtained by interview for epidemiologic purposes. Am. J. Epidemiol. 118: 583–591 (1983).
53. Bond, G. G., Bodner, K. M., Sobel, W., Shellenberger, R. J., and Flores, G. H. Validation of work histories obtained from interviews. Am. J. Epidemiol. 128: 343–351 (1988).
54. Hoar, S. K., Morrison, A. S., Cole, P., and Silverman, D. T. An occupational and exposure linkage system for the study of occupational carcinogenesis. J. Occup. Med. 22: 722–726 (1980).
55. Linet, M. S., Stewart, W. F., Van Natta, M. L., McCaffrey, L. D., and Szklo, M. Comparison of methods for determining occupational exposure in a case-control interview study of chronic lymphocytic leukemia. J. Occup. Med. 29: 136–141 (1977).
56. Guerin, M., Siemiatycki, J., Kemper, H., and Begin, D. Obtaining occupational exposure histories in epidemiologic case-control studies. J. Occup. Med. 27: 420–426 (1985).
57. Siemiatycki, J., Wacholder, S., Richardson, L., Dewar R., and Gerin, M. Discovering carcinogens in the occupational environment. Methods of data collection and analysis of a large referent monitoring system. Scand. J. Work Environ. Health 13: 486–492 (1987).