Parental Exposure to Polycyclic Aromatic Hydrocarbons and the Risk of Childhood Brain Tumors

The SEARCH International Childhood Brain Tumor Study


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Experimental evidence suggests that parental exposure to polycyclic aromatic hydrocarbons (PAH), which occurs primarily through tobacco smoke, occupational exposure, and air pollution, could increase the risk of cancer during childhood. Population-based case-control studies carried out in seven countries as part of the SEARCH Program compared data for 1,218 cases of childhood brain tumors and 2,223 controls (1976–1994). Parental occupational exposure to PAH during the 5-year period before birth was estimated with a job exposure matrix. Risk estimates were adjusted for child’s age, sex, and study center. Paternal preconceptional occupational exposure to PAH was associated with increased risks of all childhood brain tumors (odds ratio (OR) = 1.3, 95% confidence interval: 1.1, 1.6) and astroglial tumors (OR = 1.4, 95% confidence interval: 1.1, 1.7). However, there was no trend of increasing risk with predicted level of exposure. Paternal smoking alone (OR = 1.4) was also associated with the risk of astroglial tumors in comparison with nonsmoking, non-occupationally-exposed fathers. Risks for paternal occupational exposure were higher, with (OR = 1.6) or without (OR = 1.7) smoking. Maternal occupational exposure to PAH before conception or during pregnancy was rare, and this exposure was not associated with any type of childhood brain tumor. This large study supports the hypothesis that paternal preconceptional exposure to PAH increases the risk of brain tumors in humans.

brain neoplasms; child; germ cells; mutation; paternal exposure; polycyclic hydrocarbons, aromatic

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Polycyclic aromatic hydrocarbons (PAH) are a family of compounds released during incomplete combustion or pyrolysis of organic matter. The many sources of human exposure include tobacco smoke, air pollution, and occupational settings (1). Recent experimental evidence shows that paternal exposure to PAH before conception or maternal exposure during pregnancy can result in somatic or germinal mutations in the embryo that increase the risk of cancer during childhood (2–5). Alternatively, epigenetic modifications may occur in germinal or somatic cells that may result in increased cancer risk for the conceptus (6, 7).

The international case-control study coordinated by the International Agency for Research on Cancer as part of the SEARCH (Surveillance of Environmental Aspects Related to Cancer in Humans) Program offered us the opportunity to test the hypothesis that parental occupational exposure to PAH affects children’s risk of brain tumors.

MATERIALS AND METHODS

The detailed design of the SEARCH study at each center has been described in previous publications on the pooled data (8–11) and on data from individual centers (12–16). Briefly, concurrent population-based case-control studies were conducted in nine study centers (Sydney, Australia; Israel; Paris, France; Winnipeg, Canada; Milan, Italy; Valencia, Spain; Los Angeles, California; San Francisco, California; Seattle, Washington) in seven countries. The eligible cases comprised all children in those regions first diagnosed during the study period with a primary malignant tumor of the brain (International Classification of Diseases, Ninth Revision, code 191) or cranial nerves (International Classification of Diseases, Ninth Revision, code 192.0). The upper age limit at case diagnosis was 14 years in Europe and Australia and 19 years in Israel and the United States. The cases were diagnosed between 1976 and 1994; 65 percent of them were diagnosed between 1985 and 1989. Physicians and families were contacted by mail, and in-person interviews with the mother usually took place at the patient’s home. Interviews were completed for 1,218 of the 1,627 eligible cases (75 percent). Histologic confirmation of the diagnosis was obtained for 90 percent of participating cases; the other cases were assigned to a morphologic group based on the radiologic diagnosis.

Randomly selected controls from the general population were either pair-matched (six centers) or frequency-matched (three centers) to cases by sex and birth year (or by age at one center). The different study centers used several different sampling frames to contact and recruit control participants; these included census data, telephone directories, and random digit dialing methods. Eligible families were those known to have at least one eligible child according to the protocol applied in each center. Of the 2,950 eligible control families contacted, 2,223 (75 percent) were interviewed.

Mothers, and fathers whenever possible, were interviewed in their homes (or by telephone for some fathers) according to a structured questionnaire. Questionnaires used were similar at all centers. A number of suspected risk factors for childhood brain tumors were investigated, including exposure to tobacco smoke and parental occupational history. Specifically, all jobs held for at least 1 month during the 5-year period before the child’s birth were recorded, and parents were asked to describe the tasks performed at each job site and to report the type of industry, the number of hours worked weekly, and the products handled. Overall, 48 percent of the fathers who were employed during the 5-year period participated in the occupational interviews (55 percent among cases, 45 percent among controls). This percentage was much higher at the US centers (81 percent), where fathers were usually interviewed by telephone after the interview with the mother. When fathers did not participate, answers about paternal occupational history provided by the mothers were used in the analysis.

Occupations were coded according to the International Standard Industrial Classification of All Economic Activities (ISIC) (17) and the International Standard Classification of Occupations (ISCO) (18). Exposure to PAH was estimated with a job exposure matrix first developed for an international collaborative study of laryngeal cancer in Southern Europe (19). Because the original job exposure matrix did not contain all of the ISIC-ISCO combinations found in our study, the group of experts who created it prepared an extension so that every industry-occupation combination in our study had a PAH exposure level. The calendar period considered was 1974 onward. Exposure categories were defined as follows—level 1: job-related exposure is not higher than that for the general population; level 2: the job may entail a cumulative exposure higher than that for the general population; level 3: the job may entail exposure to levels definitely higher than those for the general population, but an imprecise job description does not permit discrimination between the exposed and those not exposed. This category was further subdivided according to the a priori probability of exposure (level 3a: probability less than one third; level 3b: probability between one third and two thirds; level 3c: probability greater than two thirds). There were two additional categories—level 4: the job entails exposure to the specific agent at levels clearly higher than those of the general population; and level 5: the job entails exposure to the specific agent, and exposure is known to be particularly high. Exposure levels were thus defined by both the probability of exposure and the intensity of exposure. That is, as the category level increases, the likelihood of misclassification decreases and the intensity of exposure increases. If a causal association exists, risk should increase for each category. To obtain sufficient numbers in each category, we combined the original classifications into three groups: no exposure (level 1), medium exposure (levels 2–3b), and high exposure (levels 4–5c).
at the child’s birth and parents’ educational level were very similar for cases and controls. Similarly, the average number of occupations reported during the 5-year period before birth did not differ significantly between cases (1.52 (standard error, 0.03) for fathers; 1.30 (standard error, 0.03) for mothers) and controls (1.46 (standard error, 0.02) for fathers; 1.25 (standard error, 0.02) for mothers).

Occupations considered by the job exposure matrix to entail high exposure to PAH in our population were (by decreasing numbers) motor-vehicle or aircraft engine mechanics, toolmakers and machine-tool operators, some farmers and agricultural workers, welders, some construction workers (roofers, cement finishers, etc.), cooks, equipment operators, plumbers and pipe fitters, and sheet-metal workers. Occupations considered to involve exposure at a low level were motor-vehicle drivers, warehouse porters, machinery fitters, bricklayers or paviers, some categories of agricultural workers, printers, and janitors.

Maternal occupational exposure to PAH during pregnancy was rare and was not associated with a significant excess of any type of childhood brain tumor (table 2). Odds ratios were greater than 1 for every tumor group among mothers who smoked and were occupationally exposed in comparison with nonsmoking, non-occupationally-exposed mothers, but these increases disappeared after adjustment for paternal preconceptional exposure to PAH (from smoking or from the occupation). When maternal occupational exposure before conception was considered, no increase in risk was observed for any tumor group.

Paternal occupational exposure to PAH before the child’s conception was associated with increased risks of all childhood brain tumors (odds ratio (OR) = 1.3, 95 percent confidence interval (CI): 1.1, 1.6) and astroglial tumors (OR = 1.4, 95 percent CI: 1.1, 1.7) (table 3). However, there was no evidence of an increase in risk with increasing exposure level either in two categories (medium and high) or in the original five levels of exposure (all tumors—level 1 (referent): OR = 1; level 2: OR = 1.4 (95 percent CI: 1.1, 1.8); level 3a: OR = 1.2 (95 percent CI: 0.8, 1.7); level 3b: OR = 1.2 (95 percent CI: 0.9, 1.7); level 3c: OR = 1.5 (95 percent CI: 1.1, 2.2); level 4: OR = 1.3 (95 percent CI: 1.1, 1.7); level 5: OR = 1.2 (95 percent CI: 0.6, 2.4)). The risk associated with occupational exposure in the astroglial tumor group increased when fathers who smoked were excluded (OR = 1.7, 95 percent CI: 1.3, 2.3). The magnitude of the effect of smoking alone (OR = 1.4) was smaller than the risk associated with occupational exposure with (OR = 1.6) or without (OR = 1.7) smoking, but there was no evidence that risk increased among fathers who smoked and were occupationally exposed. Center-specific risk estimates for paternal occupational exposure to PAH ranged from 1.1 (Los Angeles) to 2.3 (Valencia). There was no statistically significant heterogeneity between centers ($\chi^2 = 11.04$, $p = 0.20$). When risks were estimated separately for the four groups of age at diagnosis (0–4, 5–9, 10–14, and ≥15 years), there was no evidence of interaction between age and paternal exposure to PAH.

Validation of paternal exposure to PAH as derived from maternal reports about the father’s occupational history was possible in a subset of interviews from the US centers. For 103 families (90 control families and 13 case families),
information on paternal occupational history was obtained from both mothers and fathers. Among controls, 12 fathers were misclassified by the mother’s report: six unexposed fathers were classified as exposed to PAH, and six exposed fathers were classified as unexposed. This provides an estimate of the amount of misclassification introduced by using mothers’ reports. Among cases’ families, numbers were too small to infer the amount of misclassification. Assuming nondifferential error, we could estimate the impact of this misclassification by computing a corrected odds ratio for all tumors combined (OR = 1.4) as a Mantel-Haenszel combination of stratum-specific estimates (OR = 1.3 (from answers given by the fathers) and OR = 1.5 (the corrected odds ratio derived from answers given by the mothers)).

We also restricted the analysis to US centers, from which 44 percent of the cases originated and which used similar control selection and interview procedures. The risk estimates obtained (OR = 1.3, 95 percent CI: 1.0, 1.7) were very close to those observed in the rest of the study population (OR = 1.4, 95 percent CI: 1.1, 1.7) for paternal exposure to PAH.

**DISCUSSION**

Our results provide evidence that paternal preconceptional exposure to PAH from either tobacco smoking or occupational exposure could increase the risk of brain tumors, especially astroglial tumors, in children. No similar effect was observed for maternal smoking or maternal occupational exposure to PAH before conception or during pregnancy.

These results from a large representative sample corroborate our previous findings from European centers (20). They accredit, for a narrower class of chemicals (the PAHs), the hypothesis proposed by Fabia and Thuy (21) in 1974 and confirmed (22–27) and refuted (28, 29) by subsequent studies. Since then, experimental findings have suggested mechanisms for these associations in humans.

Much of this evidence is based on biologic markers of PAH binding to DNA. Such markers were not available in our epidemiologic study. The absence of direct measurements of PAH exposure from all possible sources precludes too strong an interpretation of our findings. Of the three principal sources of PAH exposure in industrialized countries—
tobacco smoke, occupational exposure, and air pollution—we could estimate exposure for only the first two.

Our estimate of occupational exposure to PAH was indirect. Exposure to PAH in the workplace typically occurs via products or combustion fumes originating from incomplete combustion, pyrolysis, or pyrosynthesis of organic matter. The list of occupations entailing PAH exposure higher than that in the general population was identified some time ago, but individual assessment of exposure requires detailed workplace descriptions or ad hoc measurements. Self-reports could identify circumstances of exposure to oil or coal products or combustion products, but they are limited by the lack of relative or objective benchmarks against which to judge one’s working conditions (30); this results in very variable sensitivities. An additional problem in our data is that only 48 percent of working fathers provided answers about their own occupational exposures. This explains why our assessment was preferably based on the evaluation provided by a job exposure matrix, assuming that answers from the mothers would be of better quality with regard to the father’s occupational history than when mothers were reporting specific exposures present in the father’s workplace. Use of job exposure matrices introduces a high level of misclassification, since the heterogeneity within job and industry and individual exposure determinants are not accounted for, but this misclassification would be expected to be similar among cases and controls. We used different levels of exposure corresponding to increasing levels of both probability of exposure in a given job and intensity of exposure. However, there was no suggestion of increasing risk with increasing exposure levels. The absence of a dose-response pattern may have several alternative explanations: exposure misclassification, no association between PAH exposure and cancer risk, or a nonlinear shape in the relation, as discussed below.

One may also question the validity of applying a job exposure matrix originally developed in Southern Europe to other parts of the world such as Australia, Israel, or the US West Coast. However, these countries have similar levels of industrial development and similar occupational processes, and all circumstances of occupational exposure to PAH have been

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**Table 1. Continued**

<table>
<thead>
<tr>
<th>Maternal age (years) at child's birth</th>
<th>Cases (n = 1,218)</th>
<th>Controls (n = 2,223)</th>
<th>Odds ratio</th>
<th>95% CI</th>
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<tbody>
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<td>%</td>
<td>No.</td>
<td>%</td>
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<td>Employment during the 5-year period</td>
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<td>Father</td>
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* SEARCH, Surveillance of Environmental Aspects Related to Cancer in Humans; CI, confidence interval.
† Age at diagnosis for cases; age at reference date for controls.
considered by experts when updating the job exposure matrix.

Using a validation subsample, we could verify that the use of maternal reports for paternal occupational history had only a minimal impact on the overall risk estimate.

Occupational exposure to PAH was frequent: overall, 40 percent of the control fathers were classified as probably exposed and 19 percent as more highly exposed; these percentages are similar to those estimated with this job exposure matrix in previous applications (20, 31). Exposure to PAH occurred mainly among blue-collar workers, and the percentages are similar to those estimated with this job exposure matrix.

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explored the likelihood of epigenetic tumor causation after PAH exposure; hence, this possibility cannot be ruled out (6, 7).

In our study, the risk of brain tumors in children was greater among fathers who were occupationally exposed than among fathers who smoked, in comparison with fathers who had neither exposure. However, this risk did not increase when fathers were exposed both occupationally and through smoking or when the level of estimated occupational exposure increased. Ji et al. (32), in studying paternal smoking, noted that patterns of increase in risks of childhood cancer were less consistent with the number of cigarettes smoked per day (analogous to intensity) than with the duration of smoking. These observations may well be related to the saturation in DNA adduct formation that has been demonstrated at high levels of PAH exposure (36).

In summary, the findings of our large study support the hypothesis that paternal preconceptional exposure to PAH may increase the risk of brain tumors in humans. Moreover, several reports linking PAH exposure and germ-cell damage provide indirect support for this association. It would be difficult to obtain large-scale confirmation that this mechanism operates in a portion of childhood brain tumors—by measuring PAH-DNA adducts, for example. Nonetheless, attempts at this sort of biologic confirmation must be incorporated into future studies.

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