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Parental occupational exposure to engine exhausts and childhood brain tumors

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Childhood brain tumors (CBT) are the leading cause of cancer death in children; their risk factors are still largely unknown. Since most CBTs are diagnosed before five years of age, prenatal exposure and early postnatal factors may be involved in their etiology. We investigated the association between CBT and parental occupational exposure to engine exhausts in an Australian population-based case–control study. Parents of 306 cases and 950 controls completed detailed occupational histories. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for both maternal and paternal exposure in key time periods. Increased risks were observed for maternal exposure to diesel exhaust any time before the child's birth (OR 2.03, 95% CI 1.09–3.81) and paternal exposure around the time of the child's conception (OR 1.62, 95% CI 1.12–2.34). No clear associations with other engine exhausts were found. Our results suggest that parental occupational exposure to diesel exhaust may increase the risk of CBT.

Malignant brain tumors are the leading cause of cancer mortality in children.[1,2] Despite decades of research, risk factors for childhood brain tumors (CBT) are largely unknown. Associations with some genetic syndromes and ionizing radiation have been established, but these account for only a small percentage of cases.[1–3] Since most CBT occur before five years of age, prenatal exposure and early postnatal factors may be involved in their etiology.

Paternal employment in industries involving exposures to polycyclic aromatic hydrocarbons (PAH) was first suggested as a risk factor for CBT in 1974 and has been observed in several studies since.[1,4,5] PAH are formed during incomplete burning of organic substances (*e.g.* fuel or tobacco). Few studies have assessed maternal exposures. There is some evidence for genetic and epigenetic mechanisms following preconceptional and *in utero* exposures.[1,6]

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We investigated the association between CBT and parental occupational exposure to engine exhausts in our nation-wide Australian case–control study of CBT (Aus-CBT).

Methods

Study population

Incident cases (aged 0–14 years) were identified through all ten pediatric oncology centers in Australia. Patients were diagnosed between 2005 and 2010. Three controls, frequency matched by age, sex and state of residence, were recruited for each brain tumor case. The control group consisted of two subgroups. The first group of controls was recruited specifically for the Aus-CBT study, by random digit dialing, in 2007–2010. The second set comprised controls from the Australian childhood acute lymphoblastic leukemia (Aus-ALL) study,[7] to increase statistical power at no additional cost. These controls were selected in 2005–2006 by the same method. Written informed consent was obtained from all parents and Ethics approval was granted by all participating hospitals.

We were notified of 794 CBT cases, of whom 64 were ineligible (36 with no English-speaking parent, 23 non-residents and five with no biological parent available). Of the 730 eligible cases, 568 (77.8%) were invited to take part by a physician. Based on medical or psychosocial reasons, the physicians chose not to invite the other 162. Parents of 374 cases consented (65.8% of invited, 51.2% of eligible). Information on occupational history was provided by 302 (80.7%) consenting case mothers and 247 (66.0%) consenting case

Short Report

What's new?

The causes of childhood brain tumors are largely unknown, but because they generally appear before age 5, prenatal factors seem likely to play a role. In this study, the authors collected data on the occupations of parents of children with and without brain tumors. Parental exposure to diesel exhaust, they found, increased likelihood of childhood brain tumors. Both maternal and paternal exposure increased the tumor risk, while exposure to other types of engine exhausts had no effect.

fathers. Three thousand six hundred twenty-four families of eligible control children were identified, of whom 2,255 (62.2%) agreed to participate. In accordance with our frequency-matching quotas, 1,467 of these families were recruited to the study. Occupational information was provided by 941 control mothers (64.1% of recruited) and 799 fathers (54.5%).

Data collection

All parents received a postal questionnaire which asked about residence, smoking, alcohol consumption, medical history and information about all jobs held for more than six months. A calendar including residential address served as an "anchor" to facilitate more accurate recall of past events. For each job, subjects were asked the year started and finished, job title, employer, main tasks and hours worked per week. Sets of additional detailed questions about tasks undertaken were selected for jobs involving potential exposure to agents of interest. These job-specific modules were subsequently asked in computer-assisted telephone interviews.

Exposure assessment

We assessed parental occupational exposure to engine exhaust (yes/no) based on the job characteristics obtained in the telephone interviews. Instead of using case-by-case expert assessment, as in the related Aus-ALL study,[8] two authors (DG and SP) created *a priori* exposure rules. This approach was similar to the decision-rule based method for diesel exposure described by Pronk *et al.*[9] In our study, we examined exposure to diesel, petrol and other exhaust (exhaust from engines running on propane, liquefied petroleum gas (LPG) or coal).

Exposure variables were created for specific time periods: exposure any time before birth of the child; exposure during the two years before birth; exposure during the year before birth and exposure in the year after birth (mothers only). The restriction of exposure to two years and one year before birth aimed to encompass the times of conception and pregnancy. The year after birth represented the time of breast feeding.

Statistical analyses

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (CI) for maternal and paternal exposure with risk of brain tumors in their offspring. All models were adjusted for the matching variables. In addition, maternal models were adjusted for any maternal alcohol use during pregnancy. Other potential confounders we considered were any paternal alcohol use in the year prior to pregnancy, any paternal smoking in the year prior to pregnancy and any maternal smoking during pregnancy, and maternal age at child's birth, but the addition of these variables changed the ORs by less than 5% so they were not included in the final models. Analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC).

Results

In total, 306 patients and 950 controls (532 newly recruited and 418 from the Aus-ALL study) were included in our analysis (Table 1).

Maternal occupational exposure to diesel exhaust any time before birth was associated with CBT risk (OR 2.03, 95% CI 1.09–3.81; Table 2). Although ORs for exposure during the one year or two years before birth were also increased, these CIs were very wide. Positive associations were seen for paternal exposure to diesel exhaust any time before the child's birth (OR 1.38, 95% CI 1.02–1.86), in the year before the birth (OR 1.49, 95% CI 1.01–2.19) and in the two years before birth (OR 1.62, 95% CI 1.12–2.34).

When children with paternal exposure to diesel exhaust were excluded, the OR for maternal exposure any time before birth was 2.87 (95% CI 1.29–6.37, based on 15 exposed controls and 12 exposed cases (data not shown)). This indicates that maternal occupational exposure to diesel exhaust may lead to an increased risk of CBT, independent of paternal exposure. When both parents had occupational exposure to diesel exhaust any time before the child's birth, the OR for CBT was 1.45 (95% CI 0.51–4.18, based on 14 exposed controls and 5 exposed cases), compared with non-exposed (data not shown).

Mothers' occupational exposure to petrol and other exhaust was rare ($\leq$5 subjects were exposed during the year before birth). For fathers, there was some suggestion that exposure to petrol exhaust any time before the child's birth increased CBT risk (OR 1.31, 95% CI 0.92–1.87; Table 3). Petrol and diesel exhaust exposure were moderately correlated ($R = 0.54$). The effect of exposure to petrol exhaust attenuated when both exposures were included in one model, while the estimate for diesel exhaust remained unchanged (data not shown). We found no associations with occupational exposure to other exhausts.

Discussion

Both maternal and paternal exposures to diesel exhaust before the child's birth were (independently) associated with

Table 1. Characteristics of childhood brain tumor case–control study (Aus-CBT) participants

		Case	Control
Children		306	950
Sex	Male	183 (59.8%)	500 (52.6%)
	Female	123 (40.2%)	450 (47.4%)
Age at case diagnosis or control recruitment	(mean years)	7.0	6.2
Year of birth	(median)	2001	2001
State of residence	Australian Capital Territory	4 (1.3%)	24 (2.5%)
	New South Wales	99 (32.4%)	262 (27.6%)
	Northern Territory	1 (0.3%)	11 (1.2%)
	Queensland	56 (18.3%)	221 (23.3%)
	Southern Australia	18 (5.6%)	67 (7.1%)
	Tasmania	12 (3.9%)	18 (1.9%)
	Victoria	74 (24.2%)	233 (24.5%)
	Western Australia	42 (13.7%)	114 (12.0%)
Case histology	Low grade glioma	146 (47.7%)	–
	High grade glioma	27 (8.8%)	–
	Embryonal tumor	72 (23.5%)	–
	Germ cell tumor	20 (6.5%)	–
	Ependymoma	22 (7.2%)	–
	Other/unclassified	19 (6.2%)	–
Control type	Aus-CBT	–	532
	Aus-ALL	–	418
Mothers in study		302	941
Maternal age at birth child	(mean)	30.3	31.3
Maternal smoking in birth year	Yes	50 (16.6%)	138 (14.7%)
	No	252 (83.4%)	803 (85.3%)
Maternal alcohol drinking during pregnancy	Yes	91 (30.1%)	362 (38.5%)
	No	211 (69.9%)	579 (61.5%)
Fathers in study		247	799
Paternal smoking in year prior to the pregnancy	Yes	80 (32.4%)	229 (28.7%)
	No	167 (67.6%)	570 (71.3%)
Paternal alcohol drinking in year prior to the pregnancy	Yes	221 (89.5%)	719 (90.0%)
	No	26 (10.5%)	80 (10.0%)

an increased risk of CBT. No clear associations with occupational exposure to petrol and other engine exhausts were found.

Obtaining detailed job histories from all parents allowed us to assess occupational exposures in specific time periods relative to the child's birth. The highest increased risk was observed for diesel exposure during the two years before the birth, covering the time of the child's conception. The association with paternal exposure to diesel exhaust any time before birth attenuated when fathers exposed in the year before birth were excluded (data not shown), suggesting that paternal exposure around the time of conception was most important. A similar distinction between effects of maternal exposure before conception and during gestation could not be made because of the small numbers of exposed mothers.

It is important to assess all possible health effects of diesel exhaust, as exposure is widespread and in a recent reevaluation, the International Agency for Research on Cancer classified it as a human carcinogen.[10] Emissions from diesel engines are a complex mixture of gases and particles, but evidence that whole diesel-engine exhaust induces cancer in humans through genotoxicity was considered strong.[10] PAH may be the important component of diesel exhaust in relation to CBT, as an association of paternal PAH exposure with CBT has been observed previously.[4] Prenatal exposure to PAH, through the mother's exposure, was also suggested

Table 2. Parental occupational exposure to diesel exhaust in different time periods relative to the birth of their child

	Mothers			Fathers		
Exposure time period	Cases/controls	OR	95% CI	Cases/controls	OR	95% CI
Any time before birth						
Non-exposed	285/912	1.00	ref.	149/537	1.00	ref.
Exposed	17/29	2.03	1.09–3.81	98/262	1.38	1.02–1.86
In the two years before birth						
Non-exposed	298/934	1.00	ref.	194/675	1.00	ref.
Exposed	4/7	1.72	0.49–6.10	53/124	1.62	1.12–2–34
In the year before birth						
Non-exposed	299/935	1.00	ref.	201/683	1.00	ref.
Exposed	3/6	1.54	0.37–6.42	46/116	1.49	1.01–2.19
In the year after birth						
Non-exposed	301/938	1.00	ref.			
Exposed	1/3	1.26	0.13–12.4			

Maternal models adjusted for frequency matching variables (child's sex, age at diagnosis, and state of residence) and maternal alcohol drinking during pregnancy. Paternal models adjusted for frequency matching variables (child's sex, age at diagnosis and state of residence).

Table 3. Paternal occupational exposure to petrol and other exhaust in different time periods relative to the birth of their child

		Fathers		
	Exposure time period	Cases/controls	OR	95% CI
Petrol exhaust	Any time before birth			
	Non-exposed	192/652	1.00	ref.
	Exposed	55/147	1.31	0.92–1.87
	In the two years before birth			
	Non-exposed	226/747	1.00	ref.
	Exposed	21/52	1.43	0.84–2.45
Other exhaust[1]	Any time before birth			
	Non-exposed	211/706	1.00	ref.
	exposed	36/93	1.28	0.84–1.95
	In the two years before birth			
	Non-exposed	234/766	1.00	ref.
	Exposed	13/33	1.29	0.66–2.51

Paternal models adjusted for frequency matching variables (child's sex, age at diagnosis and state of residence).
[1]Exhaust from engines running on propane, LPG or coal.

to alter global DNA-methylation, which has been associated with increased cancer risk.[11]

Diesel technology has improved over the last two decades, resulting in lower emissions. However, this improvement mainly concerns trucks and buses; non-road applications (*e.g.*, ships or heavy duty equipment used in mines and construction) are still largely uncontrolled.[12] The latter, as well as many older on-road vehicles still in use, will therefore be responsible for ongoing and substantial emission of diesel exhaust. Moreover, the potential carcinogenicity of new generation diesel engines is as yet unclear. Our results relate to relatively recent exposures as we studied young parents. The median year of exposure any time before birth was 1990, and the median birth year of children in our study was 2001.

Parents of cases may consider past exposures more than control parents, so recall bias may result in overestimated relative risk estimates.[13] However, we used information on jobs and tasks instead of self-reported exposures, where the latter is more prone to recall bias.[14] Additionally, engine exhausts are not a known risk factor for CBT, so we regard differential exposure misclassification to be improbable.

Our results suggest that parental occupational exposure to diesel exhaust before a child's birth may increase the risk of CBT.

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