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ORIGINAL ARTICLE

Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group

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ABSTRACT

Objectives We examined associations between parental occupational chemical exposures up to 10 years before conception and the risk of sporadic retinoblastoma among offspring.

Methods In our multicentre study on non-familial retinoblastoma, parents of 187 unilateral and 95 bilateral cases and 155 friend controls were interviewed by telephone. Exposure information was collected retroactively through a detailed occupational questionnaire that asked fathers to report every job held in the 10 years before conception, and mothers 1 month before and during the index pregnancy. An industrial hygienist reviewed all occupational data and assigned an overall exposure score to each job indicating the presence of nine hazardous agents.

Results We estimated elevated ORs for unilateral and bilateral retinoblastoma among offspring of fathers who were exposed to polycyclic aromatic hydrocarbons or paints in the 10 years before conception. However, only for exposure to paints did confidence limits exclude the null for bilateral disease (OR: 8.76, 95% CI: 1.32 to 58.09). Maternal prenatal exposure to at least one of the nine agents was related to increased risk of unilateral disease in their children (OR: 5.25, 95% CI: 1.14 to 24.16). Fathers exposed to at least one of the nine agents and who were ≥ 30 years of age were at increased risk of having a child diagnosed with bilateral retinoblastoma (OR: 6.59, 95% CI: 1.34 to 32.42).

Conclusions Our results suggest a role for several hazardous occupational exposures in the development of childhood retinoblastoma.

INTRODUCTION

Retinoblastoma is the leading eye cancer affecting children worldwide with an incidence of 11.8 per million children aged 0–4 years in the USA.¹ It results from an inactivation of both alleles of the *RB1* gene, a tumour suppressor gene located on chromosome 13, and produces a malignant tumour of the retina that can occur in one eye (unilaterally) or in both eyes (bilaterally).² Retinoblastoma is diagnosed very early in life; thus, the economic cost and social burden associated with this disease is substantial. In most cases, this tumour results in partial or complete vision loss.³

About 6%–10% of retinoblastoma cases are due to inherited mutations, in which one mutated allele is inherited from a parent (with the mutation in the

Key messages

What is already known about this subject?

- ▶ Previous studies have reported an increased risk of retinoblastoma among children of fathers who work with paints, pesticides and/or certain metals.
- ▶ To date, no study has reported on maternal occupational exposures and risk of retinoblastoma.

What are the new findings?

- ▶ Maternal occupational exposure to any hazardous agent, including either chemicals or radiation, in the month before or during pregnancy was associated with risk of unilateral retinoblastoma in children.
- ▶ Paternal occupational exposure to paints up to 10 years before the index pregnancy was found to increase risk of bilateral retinoblastoma in children.

How might it impact on clinical practice in the foreseeable future?

- ▶ This report indicates that preventable physical and chemical occupational exposures may substantially increase the risk of childhood retinoblastoma.
- ▶ These findings point to the necessity to evaluate the adequacy of current occupational and environmental health standards and practices in protecting the offspring of workers exposed to low-level radiation, paints, pesticides and metals.

parent's germline, eg, existing in every cell of their body); the second mutated allele is a sporadic, or new, mutation occurring in one cell of the retina (and these will not be passed down to offspring).⁴ In all other cases, inactivation of both alleles occurs from sporadic mutations. Within sporadic cases of retinoblastoma, approximately 30% have one de novo allele mutation occurring before conception in the parental germline cells or very early on in embryonic development, and one mutation occurring after conception. In the majority (>85%) of these cases, it is the father's allele in which this germline mutation occurs.⁵ These cases typically present bilaterally and given the role of the paternal



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germline cells, the father's exposures before conception are of particular interest. Alternatively, in approximately 60% of cases, retinoblastoma results from two somatic mutations (that cannot be passed down) of the *RB1* gene occurring after conception and leads to unilateral disease. These somatic changes occur during pregnancy or very early in life, and thus maternal or early childhood exposures are likely the most relevant risk factors.

Few studies have examined risk factors for sporadic retinoblastoma. Some suggest that paternal work activities, including those in agriculture, metal working and painting, are associated with sporadic cases.^{6–9} Maternal occupation has been studied far less and only one study attempted to estimate the risk of sporadic retinoblastoma associated with maternal occupational exposures; however, due to the small number of exposed women no estimates were reported.⁶

We examined associations between paternal occupational exposures experienced up to 10 years before the index pregnancy and maternal exposures experienced in the 1 month before and during pregnancy, and the risk of sporadic bilateral and unilateral retinoblastoma in children.

METHODS

Subject recruitment

We recruited unilateral and bilateral sporadic retinoblastoma cases that were diagnosed at Wills Eye Hospital in Philadelphia or at a USA or Canadian institution that is a member of the Children's Oncology Group (COG) (including over 200 medical centres) between 1 June 2006 and 30 June 2012. Detailed methods were previously published.¹⁰ Briefly, study approval was obtained by each participating COG institution, Wills Eye Institute, the University of Pennsylvania and the University of California, Los Angeles. After initial approval by a physician to contact a patient, eligibility included residing in the continental USA, Alaska or Canada, having at least one parent who spoke English or Spanish, and having at least one biological parent available to participate in the study. Children conceived with a donor egg or sperm could participate. Eligible cases had biological samples taken and analysed to ensure that their *RB1* mutation occurred sporadically and was not inherited from either parent or mosaic. Trained personnel, who could not be blinded to the case-control status of participants, conducted interviews by phone. Written consent was obtained for blood and saliva sample collection, and verbal consent was collected during telephone interviews.

Researchers initially attempted a population-based recruitment strategy for controls using birth certificates; however, this method proved unsuccessful due to low response rates. Therefore, case families were asked to nominate an age-matched control that was the child's friend or relative and under 15 years of age. For unilateral cases, mothers could not be biologically related to the female adult from the selected control family and for bilateral cases, fathers could not be biologically related to the male adult. Investigators examined the list of potential controls given by each case family and attempted to recruit the child who was closest in age to the matched case. At the end of the recruitment period, participating institutions identified 130 bilateral retinoblastoma cases, of which 35 were excluded due to mutation testing revealing an inherited *RB1* mutation or mosaicism (n=8), refusal to participate (n=25), inability to locate (n=1) or ineligibility (n=1). Of the 242 unilateral cases identified, 55 were excluded due to refusal to participate (n=42), inability to locate (n=7), inherited *RB1* mutation (n=5) or ineligibility (n=1). The study originally identified 218 controls and excluded

63 due to refusal to participate (n=61) or ineligibility (n=2). In some instances, the researchers accepted controls that were either not age matched (n=11, 7.1%) or who were biological relatives (n=1, 0.6%). Proxy interviews were conducted for 13 (3%) mothers and 66 (16%) fathers, and typically the proxy was the other parent.

At the end of recruitment, 282 cases of sporadic retinoblastoma (187 unilateral and 95 bilateral) and 155 friend controls had completed the interview.

Exposure assessment

The occupational questionnaire asked each father to recall every job held in the 10 years before conception by job title, including part time, full time and seasonal jobs. For each job, the fathers were asked to recall the number of hours they worked per week and how many months out of the year they worked. Exposure-related questions were open ended and asked:

What did [employer] make or what services did they provide?'

'What were your main activities or duties as a [job title] at [employer]?''

'What kinds of chemicals or materials, if any, did you handle, not including standard office materials?'

'What kinds of tools and equipment, if any, did you use, not including computers or standard office equipment?'

The same questionnaire was administered to mothers; however, only jobs held in the month before and during pregnancy of the index child were considered in the analyses as exposures during this time period are thought to be most relevant to the development of disease.

Parental occupational agents of interest were the same as in a previous study of paternal occupational exposures and sporadic bilateral retinoblastoma⁷ and included pesticides, welding fumes, non-welding metals, sulfur dioxide (SO₂), polycyclic aromatic hydrocarbons (PAH), ionising radiation, paints, chlorinated and non-chlorinated volatile organic compounds (VOCs) and non-paint VOCs. These agents have previously been associated with risk for childhood cancers.^{7 9 11–17}

A trained industrial hygienist, who was blinded to case status, reviewed all occupational data and assigned exposure ratings for exposure probability (1≤50%; 2=50%–80%; 3≥80%), intensity (1=low; 2=moderate; 3=high) and frequency (1=once per week or less; 2=some part of most days; 3=most of the time) for each job held. Based on these subscores, a final (overall) score was given for each hazardous exposure derived from her judgement (1=low/no exposure; 2=moderate exposure; 3=high exposure).

All analyses used the overall scores, categorising subjects as 'exposed' if they were assigned a rating of 2 (moderate) or higher. Both broad (10 years) and narrow (6 months before conception) time windows for the exposure scores were examined, as the aetiologically important time window for the effect of paternal exposures and risk of childhood cancers is unknown. Both a maximum exposure score ('any-prior' exposure) and a time-weighted average score were calculated for each agent of interest. Time-weighted averages were derived by multiplying the number of hours at each job by the overall exposure score for that job, and dividing it by the total number of hours worked in the time window of interest (10 years or 6 months):

$$\text{Time weighted average} = \frac{\sum \text{number of hours at a job} * \text{job exposure score}}{\text{Total number of hours worked}}$$

The number of hours worked at each job was calculated by multiplying hours worked per week by number of weeks worked per year by number of years worked. This assumes that the assigned exposures occurred uniformly throughout the duration

of each job. For these time-weighted averages, an exposure score ≥ 1.5 was considered the threshold for calling someone exposed to the particular agent of interest. An additional sensitivity analysis was conducted using a score of ≥ 2 as the threshold for being exposed so as to maintain consistency with analyses that used maximum exposure scores.

Since not all cases were age matched to controls, we controlled for age in our unconditional analyses. Given that several studies have linked paternal age to increased risk of retinoblastoma,^{18–21} and that this relationship may not necessarily be linear, we included categories of paternal age a priori as a covariate in adjusted models (<25, 25–29, 30–34, 35–39, 40+ years). Other variables that altered effect estimates by more than 10% were included in our adjusted models, that is, smoking status (never smoked; smoked in the year before pregnancy; smoked, but not in the year before pregnancy), race/ethnicity (white, non-Hispanic; black, non-Hispanic; Hispanic; other), income (<\$25 000; \$25 000–\$49 999; \$50 000–\$99 999; \geq \$100 000) and educational attainment (less than high school; high school; post high school training or some college; college graduate; graduate level or professional school). We previously observed these factors to be associated with retinoblastoma risk in our studies,^{7 8} and smoking, race/ethnicity and education have been controlled for also in previous studies of retinoblastoma and parental occupational exposures.^{6–8} To mitigate the effects of possible over adjustment due to socioeconomic status (SES), a sensitivity analysis was conducted using a minimally adjusted model that only included paternal age and smoking status.

We attempted to use both conditional and unconditional logistic regression to evaluate the risk of retinoblastoma. However, due to the large number of cases without matched controls (n=135, 48%) and small cell counts in most occupational exposure categories, only results of the unconditional analyses are presented. We report ORs and 95% CIs for both adjusted and unadjusted models.

Risks for unilateral and bilateral retinoblastoma related to paternal occupational exposure to each agent were examined for the periods 6 months and 10 years before conception. We also conducted analyses stratified by fathers age (<30 years vs \geq 30) so as to ensure that there was a long enough work history for each father to capture relevant exposures, and also by household income (<\$75 000 vs \geq \$75 000) to attempt to account for SES differences between cases and controls. Due to the small numbers in some exposure groups, in these analyses we used ‘any’ paternal hazardous occupational exposure as the exposure variable.

Though 75% of women worked in the month before or during pregnancy, few were exposed to one of the nine hazardous agents we evaluated (n=16, 4%). Therefore, we were limited to assessing any type of chemical exposure only (occupational pesticide, paint, non-chlorinated and non-paint VOCs, PAH) and/or ionising radiation exposure. No women were exposed to welding fumes, non-welding metals, chlorinated VOCs or SO₂.

Regression models relied on different reference groups, that is, those exposed to a specific agent of interest versus those unexposed to the agent of interest. However, we also conducted sensitivity analyses examining unilateral and bilateral retinoblastoma comparing each agent of interest with a single common reference group of subjects unexposed to all agents of interest. We also performed a separate sensitivity analysis excluding proxy interviews and parents of children who were not age matched. Both maximum exposure values and time-weighted exposure values were assessed in each analysis.

Table 1 Demographic characteristics of cases (unilateral and bilateral) and controls*

	Controls (%) n=155	Unilateral RB (%) n=187	Bilateral RB (%) n=95
Father's race			
White non-Hispanic	104 (67.1)	96 (51.3)	59 (62.1)
African American/ black non-Hispanic	7 (4.5)	12 (6.4)	5 (5.2)
Hispanic	22 (14.2)	34 (18.2)	16 (16.8)
Other	9 (5.8)	25 (13.4)	11 (11.6)
Father's age at child's birth			
<25	11 (7.1)	16 (8.6)	7 (7.4)
25–29	40 (25.8)	35 (18.7)	19 (20.0)
30–34	47 (30.3)	53 (28.3)	29 (30.5)
35–39	32 (20.6)	42 (22.5)	22 (23.2)
40+	13 (8.4)	20 (10.7)	13 (13.7)
Father's smoking status			
Never smoked	94 (60.6)	91 (48.7)	57 (60.0)
Smoked in year before pregnancy	31 (20.0)	52 (27.8)	27 (28.4)
Smoked, but not in year before pregnancy	18 (11.6)	24 (12.8)	7 (7.3)
Household income			
< \$25 000	11 (7.1)	20 (10.7)	15 (15.8)
\$25 000–\$49 000	27 (17.4)	43 (23.0)	18 (18.9)
\$50 000–\$99 000	57 (36.8)	53 (28.3)	28 (29.5)
\geq \$100 000	40 (25.8)	40 (21.4)	24 (25.3)
Father's education			
Less than high school	7 (4.5)	13 (7.0)	11 (11.6)
High school	20 (12.9)	31 (16.6)	19 (20.0)
Post high school training or some college	24 (15.5)	39 (20.9)	14 (14.7)
College graduate	53 (34.2)	63 (33.7)	31 (32.6)
Graduate level or professional school	39 (25.2)	21 (11.2)	16 (16.8)

*Due to missing data, not all columns add to 100%.

RESULTS

Father's age was similar on average for cases and controls. Control parents were more likely to be white non-Hispanic, never smokers and to have graduate level or professional school education (table 1). Families of cases, especially the bilateral type, were more likely to have annual incomes of <\$25 000.

In the 10 years before conception of the index pregnancy, the average number of jobs held by case and control fathers was 2.9 (SD of 1.6 and 1.5, respectively). Table 2 displays the number of case (unilateral and bilateral) and control fathers exposed to each agent of interest as well as the related risk of disease among children. Due to small cell counts (of less than five exposed cases or controls), we were limited to performing unadjusted analyses only for certain exposures: non-welding-related metal exposures, SO₂ (unilateral), ionising radiation (unilateral), paint and non-chlorinated VOCs (bilateral). For unilateral cases, we were unable to examine associations for welding fumes and for chlorinated VOCs while for bilateral cases we were unable to examine welding fumes, SO₂, ionising radiation and chlorinated VOCs separately.

Children of fathers who had any hazardous exposure in the 10 years before conception had an elevated risk of both unilateral and bilateral retinoblastoma. For unilateral cases, increased risks were estimated for children whose fathers were exposed to PAH

Workplace

Table 2 Risk of unilateral and bilateral retinoblastoma among children whose fathers were exposed to various occupational exposures in the 10 years before conception, based on time-weighted average exposure values*

Occupational exposure	Unilateral				Bilateral			
	Exposed cases (n=187)	Exposed controls (n=155)	Crude OR (95% CI)†	Adjusted OR (95% CI)‡	Exposed cases (n=95)	Exposed controls (n=155)	Crude OR (95% CI)†	Adjusted OR (95% CI)‡
Any hazardous exposure§	32	23	1.30 (0.71 to 2.38)	1.33 (0.63 to 2.79)	21	23	2.01 (0.96 to 4.21)	2.45 (0.92 to 6.51)
Pesticide	22	20	0.95 (0.49 to 1.84)	0.99 (0.45 to 2.20)	15	20	1.27 (0.58 to 2.79)	1.46 (0.52 to 4.10)
Welding fumes	2	0	–	–	2	0	–	–
Non-welding metals	4	5	0.83 (0.21 to 3.25)	¶	1	5	0.51 (0.05 to 5.39)	¶
SO ₂	4	4	0.81 (0.20 to 3.40)	¶	0	4	–	–
PAH	15	9	1.49 (0.62 to 3.56)	1.34 (0.48 to 3.72)	7	9	1.58 (0.51 to 4.91)	1.51 (0.36 to 6.38)
Ionising radiation	2	2	0.69 (0.10 to 5.05)	¶	0	2	–	–
Paint	5	2	2.52 (0.47 to 13.57)	¶	5	2	8.76 (1.32 to 58.09)	¶
Chlorinated VOCs	3	0	–	–	0	0	–	–
Non-chlorinated VOCs	5	5	1.01 (0.28 to 3.64)	1.30 (0.28 to 6.05)	2	5	1.01 (0.19 to 6.43)	¶

*Using different reference groups for each exposure (those unexposed to chemical of interest only).

†Adjusted for child's age at interview.

‡Adjusted for father's race, age, smoking status, income and education.

§Occupational exposure to one or more of the following agents: pesticides, welding fumes, non-welding metals, SO₂, PAH, ionising radiation, paint, chlorinated VOCs and non-chlorinated VOCs.

¶Insufficient number of exposed cases/controls for providing adjusted estimates.

PAH, polycyclic aromatic hydrocarbons; VOC, volatile organic compound.

and paints, but CIs were wide due to small numbers. Exposure to pesticides, PAH and paints were also associated with increased risk of bilateral disease; however, only for exposure to paints did confidence limits exclude 1 (OR: 8.76, 95% CI: 1.32 to 58.09).

When stratifying by paternal age, the association between any exposure and bilateral disease was positive, although relatively weak, in younger fathers (under 30 years of age), but

among fathers who were 30 years or older risk was increased (adjusted OR: 6.59, 95% CI: 1.34 to 32.4) (table 3). Similarly, children of fathers who were exposed to any hazardous agent and in a higher income bracket (\geq \$75 000) were at increased risk of having a child diagnosed with unilateral disease in both crude and adjusted models (OR: 4.64, 95% CI: 1.17 to 18.5 and OR: 3.16, 95% CI: 0.57 to 17.66, respectively). Of note,

Table 3 Risk of unilateral and bilateral retinoblastoma relative to any paternal hazardous occupational exposure in the 10 years before conception, stratified by age and education

	Exposed cases	Exposed controls	Crude OR (95% CI)*	Adjusted OR (95% CI)†
Exposure to any chemical‡ and <30 years of age§				
	(n=50)	(n=51)		
Unilateral	13	13	1.02 (0.42 to 2.51)	1.89 (0.47 to 7.57)
	(n=27)	(n=51)		
Bilateral	7	13	1.06 (0.36 to 3.16)	1.12 (0.22 to 5.59)
Exposure to any chemical‡ and \geq 30 years of age§				
	(n=111)	(n=92)		
Unilateral	19	10	1.78 (0.76 to 4.14)	1.32 (0.48 to 3.61)
	(n=63)	(n=92)		
Bilateral	14	10	4.56 (1.44 to 14.5)	6.59 (1.34 to 32.42)
Exposure to any chemical‡ and income <\$75 000¶				
	(n=94)	(n=72)		
Unilateral	22	16	1.04 (0.50 to 2.20)	0.82 (0.34 to 2.00)
	(n=51)	(n=72)		
Bilateral	18	16	2.14 (0.89 to 5.16)	2.17 (0.73 to 6.47)
Exposure to any chemical‡ and income \geq \$75 000¶				
	(n=58)	(n=63)		
Unilateral	10	3	4.64 (1.17 to 18.47)	3.16 (0.57 to 17.66)
	(n=33)	(n=63)		
Bilateral	2	3	4.88 (0.53 to 45.25)	6.16 (0.18 to 209.30)

*Adjusted for child's age at interview.

†Specific adjustments made for each level of stratification.

‡Relevant exposures include pesticides, welding fumes, non-welding metals, SO₂, PAH, ionising radiation, paints, chlorinated and non-chlorinated VOCs and non-paint VOCs.

§Adjusted for father's race, smoking status, income and education.

¶Adjusted for father's race, age, smoking status and education.

PAH, polycyclic aromatic hydrocarbons; VOC, volatile organic compound.

Table 4 Risk of unilateral and bilateral retinoblastoma among children whose mothers had occupational pesticide, paint, VOC, PAH or ionising radiation exposure in the 1 month before conception or during pregnancy

Disease	Exposed cases (n=187)	Exposed controls (n=155)	Crude OR*
Unilateral	12 (n=95)	2 (n=155)	5.25 (1.14, 24.16)

paternal age and family income were only weakly correlated ($r=0.3$).

Results did not change when we used maximum exposure values rather than time-weighted averages, though CIs were wider (results not shown). Effect estimates did not change by more than 20% for any variable when we performed analyses adjusting only for paternal age and smoking status. A separate analysis comparing exposed fathers to a single reference group of fathers who were unexposed to all agents of interest revealed no difference in unilateral estimates and slightly higher point estimates for bilateral retinoblastoma, particularly for pesticide exposure (adjusted OR: 1.82, 95% CI: 0.64 to 5.19). Analyses that targeted paternal exposures 6 months before the index pregnancy only, were only able to examine pesticides, PAHs or 'any' hazardous occupational exposure due to the small number of exposed fathers, and associations between exposure and risk of unilateral or bilateral retinoblastoma were near the null with wide CIs for all exposures except PAH (OR: 1.37, 95% CI: 0.32 to 5.81). We only saw minimal (<10%) reductions in point estimates in sensitivity analyses that restricted to parents without a proxy respondent or in analyses that excluded parents of non-age-matched children.

For mothers with occupational exposures to pesticides, paints, VOCs, PAH or ionising radiation in the 6 months before conception or during pregnancy, we estimated increased risks of having a child with unilateral disease (OR: 5.25, 95% CI: 1.14 to 24.2) (table 4). For bilateral retinoblastoma, point estimates were elevated; however, due to the small number of exposed cases ($n=2$), these results were generally less stable (OR: 3.03, 95% CI: 0.31 to 29.9).

DISCUSSION

In this study, the risk of sporadic unilateral retinoblastoma increased with paternal exposure to PAH and paints and the risk of sporadic bilateral retinoblastoma increased with paternal exposure to PAH, paints and pesticides in the 10 years before conception; however, only for exposure to paints confidence limits excluded 1. Maternal occupational exposure to any of the agents (pesticides, paints, VOCs, PAH or ionising radiation) was associated with increased risk of having a child diagnosed with unilateral disease. Given the rarity of disease, we were limited to presenting results of unadjusted analyses only for most of the specific occupational exposures.

Currently, the biological mechanisms through which paternal occupational exposures may impact offspring cancer risk, including retinoblastoma, are not well understood. One proposed theory is that fathers expose women with toxic chemicals from work on their skin or clothing, thereby exposing the child (transplacentally).²² However, a more plausible mechanism is that paternal exposure to toxicants results in alterations

to the father's sperm, which could result in increased susceptibility to cancer among offspring. This is especially likely for retinoblastoma where it is well documented that specific genetic changes in the paternal germline contribute to risk of disease.⁵ Previous literature has shown that sperm are susceptible to environmental agents including lead, paint strippers and excessive heat; however, aside from infertility there is limited evidence that these exposures affect the offspring.^{23 24} One study reported that toluene, a solvent found in paint and paint thinners, results in DNA damage in the sperm of rats.²⁵ Another study found PAHs to impact the motility and viability and result in morphological abnormalities of male sperm.²⁶ Exposure to PAHs was also found to alter the nucleotide excision, and base excision repair mechanisms were used to mend damaged sperm caused by chemical agents.²⁷

Only one study found paternal employment-related pesticide exposure in both the 10 years and 1 year before conception to be associated with offspring sporadic bilateral retinoblastoma (OR: 1.64, 95% CI: 1.08 to 2.50 and OR: 2.12, 95% CI: 1.25 to 3.61, respectively).⁷ The study also found that higher levels of pesticide exposure (compared with moderate or none) relate to higher risks of bilateral disease. Several other studies, which examined both occupational and residential pesticide use by parents and risk of retinoblastoma, showed no association.^{9 13 28–30} However, these studies obtained all occupational data from birth or death records only, and thus did not have access to information such as the specific agents that parents were exposed to at work, employment dates or number of jobs held.^{6 9 28} Furthermore, most studies, while sufficiently powered to assess exposure–disease relationships among all cancer types, did not have enough data to be informative when performing subgroup analyses specifically for retinoblastoma or 'all childhood eye cancer' (of which retinoblastoma accounts for over 90%), with the total number of cases ranging from 2 to 16.^{13 28–30} Most of the abovementioned studies were unable to examine the effects of maternal or paternal exposures separately, nor were they able to distinguish between heritability and laterality of disease; therefore, the findings are not directly comparable to ours.

This study found paternal occupational exposures in the 10 years before index pregnancy to be associated with retinoblastoma risk; however, elevated risks were not seen for exposures in the year before pregnancy, with the exception of PAH, as effect estimates were all near one with wide CIs. Although spermatogenesis spans approximately 90 days, we hypothesise that longer periods of relevant exposure could lead to genetic germline mutations eventually causing disease due to cumulative damage.³¹ Long-term exposure to cigarette smoke, which emits PAHs, has been previously shown to affect both the genomic and epigenomic components of sperm, which may be associated with developmental defects in the offspring.³² Another study found that paternal exposures longer than 90 days preconception resulted in increased risk of sporadic retinoblastoma, although this study examined non-occupational medical radiation exposure.⁸ These authors suggested that these exposures may have caused mutations to occur in stem cell spermatogonia cells, which persist throughout reproductive life.⁸ Additionally, our sample only included a small number of exposed fathers (ranging from $n=3$ to $n=28$); therefore, additional studies with larger sample sizes are needed before reliable conclusions can be drawn.

Previous studies have described non-familial unilateral retinoblastoma incidence with two postconception hits to the *RB1* gene, implying that maternal exposures during pregnancy are important potential risk factors.³³ Only 18 mothers in our study

were determined to have any chemical or physical exposures in the month before or during pregnancy, and we thus had to group all occupational exposures together. Despite small numbers, we estimated increased risks for unilateral disease among exposed mothers, which is consistent with the postulated aetiology of disease. A recent case-control study of retinoblastoma found that a greater proportion of mothers in farming occupations had a child with retinoblastoma compared with controls (71% vs 32%).³⁴ A previous study examining the risk of sporadic heritable and non-heritable retinoblastoma from maternal occupations faced similar restrictions as few mothers held jobs with hazardous exposures.⁶ For non-occupational exposures, one study reporting on household pesticide use found the risk for non-heritable unilateral retinoblastoma to be increased among mothers who were exposed to insect or garden sprays during pregnancy, although CIs were wide (OR: 2.7; 95%CI: 0.6 to 15.6).³⁵ We recently reported an increased risk of unilateral disease associated with parental use of home insecticides as well as home use of professional lawn or landscape services.³⁶ Two studies examined the association between ionising radiation exposure in parents and the development of retinoblastoma in offspring, and both found that mothers who had high gonadal radiation exposure were at increased risk of having a child with sporadic bilateral retinoblastoma, although only the larger, more rigorous study was sufficiently powered.^{8 35}

Stratifying on paternal age and family income suggested stronger associations among older fathers and higher family income and risk of bilateral and unilateral disease, respectively. Several other studies have reported a link between parental age and increased risk of retinoblastoma.^{18-21 37} Only one of these studies was population based and determined that the mean age of fathers was higher among children with sporadic retinoblastoma (33.7 years) than children in the general population (32.5 years), although whether this marginal increase in age truly reflects a difference in risk is unclear.³⁷ Reproductive age may influence the risk of childhood cancer through increased mutations in the paternal germ line cells and increased chromosomal aberrations during maturation of maternal germ cells, which increase the risk of cancer development in the offspring.³⁸ Higher family income may be a proxy for more hours worked (including overtime hours) which, in turn, could increase the level of chemical exposure and, subsequently, the risk of disease.

As with all interview-based case-control studies, recall bias is a possibility. Some occupations used specialised questionnaires, though we did not have access to this data and thus these participants may not have reported all relevant substances they were exposed to. However, most occupations tend to be recalled quite accurately³⁹ and we anticipate that errors in recall of specific agents would be non-differential among cases and controls as we asked about their jobs and not specific potentially hazardous agents. An additional limitation is the possibility of overmatching due to the use of friend controls. Friend controls may have been more similar to cases on many factors that relate to SES, race, education and non-occupational exposures in the local community environment. Indeed, a previous analysis from the first stage of this study found that for demographic characteristics (race/ethnicity, education, income and paternal age) there appeared to be a greater number of concordant case-control sets than would be expected.⁴⁰ However, when reviewing potential exposures of interest, the number of concordant pairs was similar to what would be expected by chance, as determined by comparing the observed concordance to simulated data that randomly permuted the controls' demographic factors and exposures.⁴⁰ Thus, friend controls may not have resulted in overmatching

for several exposures of interest, yet it may provide cases and controls that are more closely matched on possible covariates, reducing confounding bias. Our cases and controls differed on race, smoking status and education level, possibly indicating that individuals of lower SES tend to have jobs with the highest harmful exposures. Furthermore, lower SES cases were less likely to provide the names of possible controls, who would have likely had a similar probability of harmful exposures. Thus, our control group underrepresents those of lower SES. Though we adjusted for SES, overadjustment is possible given that our SES variables (education and income) may be mediators on the pathway between exposure and disease. To account for these concerns, we performed a minimally adjusted model that included age and smoking status and found only slight differences in point estimates.

Our occupational questionnaire did not ask specifically about occupational radiation exposure, despite it being a known risk factor for retinoblastoma.⁸ However, we expect that subjects exposed to radiation are aware of this occupational hazard and that reporting is similar among parents of cases and controls. We were unable to conduct conditional regression analyses as many cases (48%) did not have a matched control. We do not anticipate this to have resulted in biased estimates as our unconditional regression analyses adjusted for child's age, the matching variable. Some participants had proxy respondents complete the questionnaire in their place. For the occupational portion of the questionnaire that was used for this paper, we anticipate that exposure-related questions would be incorrectly or only partially recalled by the proxy. However, given the relatively small proportion of interviews conducted by a proxy, only slight changes (<10%) were observed in point estimates when we excluded all proxy interviews. We also had 11 controls who were not age matched to our cases, which may have caused differences in the accuracy of jobs recalled by parents. We performed additional sensitivity analyses to account for this and found only minor (<10%) reductions in point estimates.

The limited number of studies on parental occupational exposures, particularly maternal exposures, and retinoblastoma risk suggests that our results ideally should be confirmed in larger populations. However, this will be difficult since the disease is very rare. Our study supports the notion that parental occupational exposures are preventable risk factors for the development of sporadic bilateral and unilateral retinoblastoma.

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