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A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma

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Abstract

Background—The risk factors for sporadic (i.e. non-familial) retinoblastoma remain largely unknown. However, some studies have suggested a role for paternal work activities, primarily in farming and the metalworking industry, in the development of childhood retinoblastoma.

Objectives—We examined the relationship between paternal occupational exposures from jobs held 10 years and one year prior to conception and the risk of sporadic bilateral retinoblastoma in children.

Methods—Paternal occupational data were obtained for 198 incident cases diagnosed with sporadic bilateral retinoblastoma from January 1998 to May 2006 and 245 referral-based controls from the case child's relatives and friends who were matched to 135 of the cases on birth year. Industrial hygienists independently assigned exposure scores for nine agents, including estimates of probability, intensity, and frequency as well as an overall summary exposure score. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed using logistic regression models, using the full sample of cases and controls as well as subset of cases with matched controls only.

Results—There was some indication of an elevated risk associated with paternal pesticide exposure in the 10 years prior to conception (OR= 1.64; 95% CI: 1.08-2.50) as well as in the year before conception (OR= 2.12; 95% CI: 1.25-3.61). However, results for pesticide exposure were inconsistent and varied by analysis approach. An increased risk was also observed for non-welding metal exposure during the 10 years prior to conception in the full (OR= 1.35; 95% CI: 0.86-2.12) and matched (OR= 1.40; 95% CI: 0.82-2.37) samples, but not in the year before

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conception. Exposure-response trends were observed for pesticides in the full sample (p for trend < 0.0001), and consistently across both samples for non-welding metal exposures.

Conclusions—Our findings suggest a potential role of paternal occupational exposures to non-welding metals and perhaps pesticides in the etiology of childhood retinoblastoma.

Keywords

germline mutation; retinoblastoma; child; occupational exposure; case-control studies

INTRODUCTION

Retinoblastoma is a malignant tumor of the retina that is generated by mutations in the *RB1* gene, a tumor suppressor gene located on chromosome 13 [1]. Although the incidence is low with approximately 350 new cases per year in the United States, it is the most common ocular cancer in children [2]. Retinoblastoma may occur either unilaterally (i.e., in one eye) or bilaterally (i.e., in both eyes). All bilateral retinoblastoma occurs as a result of a germline RB1 mutation, which is inherited in familial retinoblastoma and arises anew in sporadic germline retinoblastoma. The germline form of retinoblastoma comprises about 40% of all cases (25% of these are familial and 75% sporadic) and usually occurs bilaterally [3]. Germline (both familial and sporadic) retinoblastoma is caused by a constitutional RB1 mutation followed by a somatic RB1 mutation in a retinal cell. In sporadic germline retinoblastoma, the parents of the affected individual do not carry the RB1 mutation, but the affected individual has a new constitutional RB1 mutation and can pass the mutation and the disease onto his/her children. United States incidence data from 1975 through 2004 for children 0 to 4 years of age show that the unilateral form of retinoblastoma occurs approximately 73% of the time while the remaining 27% are bilateral cases [4].

The risk factors for sporadic retinoblastoma remain largely unknown. However, some studies have suggested that paternal work activities, primarily in farming and the metalworking industry, are associated with non-germline retinoblastoma [3,5] which is caused by somatic RB1 mutations. Paternal exposures are of particular interest because the new mutation in sporadic germline retinoblastoma occurs on the father's allele in about 85% of cases [6,7]. Exposures that cause somatic mutations may also cause germline mutations and thus, work activities which potentially involve such exposures were of interest in our study of sporadic bilateral retinoblastoma. Additionally, it is believed that the timing of exposures (or the critical period) in the etiology of unilateral and bilateral retinoblastomas most likely differ; therefore it is important that epidemiologic studies differentiate between the two subtypes. The critical period for sporadic bilateral retinoblastoma is presumably before the child's conception as the RB1 mutation has newly occurred in the parent and is present at the child's conception. We examined the relationship between paternal occupational exposures from jobs held 10 years prior to conception and the risk of sporadic bilateral retinoblastoma in children.

METHODS

Study Population

Details of recruitment, eligibility criteria, and data collection for this case-control study have been described previously [5,8]. In short, eligible patients were diagnosed with sporadic bilateral retinoblastoma from January 1998 to May 2006 and treated at one of the nine participating institutions in the United States and Canada. One to three matched controls free of cancer were selected based on referrals from the case child's relatives and friends in their same or adjacent age category (0-1, 2-4, 5-6, 7-9, and 10-12 years); some cases were unable

or unwilling to refer controls. Identified control fathers who were biologically related to the case father were excluded so that case-control comparisons were not influenced by familial genetic factors. The original study interviewed 203 case and 247 control fathers, from which the current study subjects were obtained.

This study was approved by the Research Subject Review Board at the University of Rochester. The original study was approved by the Institutional Review Boards of all participating institutions [5].

Exposure Assessment

Because risk factors for sporadic germline retinoblastomas are unknown, we evaluated a broad array of paternal occupational exposures, some of which have been examined in previous studies of retinoblastoma [3] and other childhood cancers [9-15]. Exposures of interest were pesticides, welding fumes, non-welding metals, sulfur dioxide (SO2), polycyclic aromatic hydrocarbons (PAH), ionizing radiation, paints, chlorinated volatile organic compounds (VOC), and non-chlorinated and non-paint VOCs. Cases and controls were randomly assigned to two members of a panel of three industrial hygienists (J.G.A, M.D.M, R.F.H.), who independently evaluated all jobs held for six months or longer during the 10 years prior to the child's conception. Thus, each rater evaluated two-thirds of all jobs held by fathers in our dataset. The two experts were blinded to case status and individually rated each job 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). Based on the compilation of these sub-scores for each job, each rater assigned a final (overall) score for each exposure agent derived from his own judgment as 1 = low/no exposure, 2 = moderate exposure, and 3 = high exposure.

The etiologically-important time window for a role of paternal exposures in the risk of childhood cancers is uncertain, although for sporadic bilateral retinoblastoma, it has been established that the first mutations occur in the father's germline which indicates that relevant exposures occur prior to the child's conception [16]. Therefore, we examined exposures in both a broad and relatively narrow time window prior to conception based on all jobs held in the 10 years prior to conception ('any prior' exposure) and exposures from jobs held any time during the 12 months prior to conception ('year before index pregnancy'). Overlap between exposures in the two time windows was assessed using Spearman's correlation coefficient among those exposed in the 10 years prior to conception.

Analyses using the overall scores considered subjects as 'exposed' if assigned a rating of moderate (score = 2) or higher from at least one rater and 'unexposed' if both raters assigned an overall score of low/no exposure (score = 1). Exposure was counted if one or more jobs in the relevant time met these criteria.

In addition to overall scores for 'any' exposure, exposures were quantified by level based on the probability, intensity, and frequency ratings of all jobs from each rater as well as the duration of each job, derived from a previously used algorithm of similar exposures [17]. Average probability, intensity, and frequency scores across the two raters were calculated for each job-exposure combination. The product of these averages and job duration (in months) for each job (i.e., probability × intensity × frequency × duration) were summed across jobs to derive a cumulative exposure score, which was subsequently divided by the total number of working months in the two exposure windows to obtain a time-weighted average exposure score. This methodology assumes that assigned exposures occurred uniformly throughout the duration of a particular job. Spearman correlation coefficients between the time-weighted average exposure scores and cumulative exposure scores were high, ranging from 0.90 to 0.98.

Individuals with low/no level of exposure would have a score of 1 for probability, intensity, and frequency for each job in the period of relevant exposure which would yield an average summary score of 1.0. This group denotes the reference group in all analyses. The remaining sample with time-weighted average summary scores from greater than 1 to 27 (which would occur if all jobs in an occupational history were assigned a score of 3 for probability, intensity and frequency) was divided in half at the 50th percentile of the distribution of summary scores; the lower half representing moderate levels of exposure and the upper half representing high levels of exposure.

To assess the reliability of exposure classification using this metric, we conducted a sensitivity analysis repeating our calculation of cumulative and time-weighted average exposures, including only jobs with an exposure probability of 50% or greater (score ≥2). That is, any job with probability less than this cut-off would be considered unexposed. Consequently, individuals who only have jobs with exposure probabilities less than 50% (score = 1) would fall in the referent category and thus the exposed would consist of those who would be more likely truly exposed.

Covariates

Since the child's birth year was the basis of matching, all analyses controlled for this variable. In addition, we selected potential confounders based on theoretical justifications and consistency with our previous analyses [5], including father's smoking status (never; former; smoked in year before index pregnancy), race/ethnicity (non-Hispanic white; non-Hispanic African-American; Hispanic; other), education level (no college degree; college degree or higher), and proxy interview (yes or no).

Statistical analysis

For exposure to each of the nine agents, we calculated the percent agreement and kappa scores [18] for each combination of raters to assess inter-rater reliability of the overall exposure scores. In addition, the prevalence of 'any' exposure was determined for each exposure agent among cases and controls during both periods of relevant exposure.

Because not every case had a matched control, we conducted regression analyses using the full unmatched sample in addition to the matched sample. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CI) were calculated using unconditional (full sample) and conditional (matched sample) logistic regression models. Statistical significance for two-sided p-values was defined as $p < 0.05$. ORs were estimated for any vs. no exposure as well as across levels of exposure based on the time-weighted average summary score: none/low (reference group), moderate, and high. P-values for trend were computed for selected exposure-response relationships using the Cochrane-Armitage method [19,20]. We also conducted analyses for cumulative exposure, which yielded similar results to the time-weighted average exposure scores in our *primary* analyses; therefore, primary findings only report average exposures while the sensitivity analyses contrast both cumulative and average exposure assessments. Some differences existed between the two metrics in our sensitivity analyses considering only jobs with an exposure probability of 50% or greater as exposed, which are noted below. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Descriptive statistics

Two hundred and three case fathers had a child diagnosed with sporadic bilateral retinoblastoma and 247 were fathers of matched controls. Of these, 198 cases (98%) and 245

controls (99%) had complete exposure information and comprised the full sample. Some families were unable or unwilling to provide any controls; therefore, 63 (32%) of the cases did not have matched controls and were excluded in the analysis of the matched sample (135 cases and 245 controls). Cases in our full and matched samples appear to have similar demographic characteristics compared to controls with respect to father's age at conception, sex of the child, and proxy interview status (Table 1). However, control parents were composed of a higher proportion of non-Hispanic whites and a smaller proportion of non-Hispanic African-Americans, were more likely to have never smoked, and were more likely to hold a college degree or higher as compared with all cases. These observed differences in race, smoking status, and education were controlled for in the analysis by inclusion of these variables in the multivariable unconditional logistic regression models or by matching. When cases without matched controls were excluded, case and control parents were more similar in race/ethnicity, smoking status, and education level, indicating that matching was effective in enhancing comparability between groups. The average number of jobs held within 10 years prior to index pregnancy and in the year before index pregnancy were 3.0 and 1.1, respectively, and were similar between cases and controls.

Any two raters agreed 77% to 99% of the time regarding the overall score for each exposure agent except for non-chlorinated/non-paint VOCs, which yielded lower agreements of 28% to 65% across any two raters. More specifically, the agreement between raters, based on the three categories of overall exposure scores, was fair to moderate for pesticides (κ = 0.39-0.60), welding fumes (κ = 0.49-0.56), non-welding metals (κ = 0.45-0.54), SO2 (κ = 0.27-0.43), PAH (κ = 0.33-0.45), ionizing radiation (κ = 0.33-0.44), and paint (κ = 0.41-0.59), and slight to fair for chlorinated VOCs (κ = 0.17-0.31) and non-chlorinated/non-paint VOCs (κ = 0.07-0.19).

Table 2 displays the prevalence of paternal occupational exposures among cases and controls from any job held in the ten years prior to index pregnancy and jobs held in the year before index pregnancy. Cases had higher prevalence of pesticide, welding fume, metal, SO2, and PAH exposures compared to controls in the ten years prior; however these differences became less apparent in the year before index pregnancy for all exposures except pesticides. Having any prior exposure to ionizing radiation, paint, and chlorinated VOCs was slightly less prevalent in cases compared to controls in the ten years prior, although the prevalence of chlorinated VOCs became similar in cases and controls in the year before the index pregnancy. Prevalence of non-chlorinated/non-paint VOCs were nearly identical between cases and controls in both exposure periods.

Exposure in the ten years prior to pregnancy

In the matched adjusted analysis (Table 3), exposure to pesticides, non-welding metals, and non-chlorinated/non-paint VOCs produced elevated ORs of 1.40 (95% CI: 0.85-2.30), 1.40 (95% CI: 0.82-2.37), and 1.52 (95% CI: 0.69-3.36), respectively. When considering the full adjusted sample, exposure to pesticides was significantly associated with sporadic bilateral retinoblastoma (OR = 1.64; 95% CI: 1.08-2.50). Risk estimates for other exposures were not meaningfully different from the null. Similar effect estimates were noted in the matched adjusted analysis except for welding fumes, which exhibited ORs close to one.

To evaluate exposure-response associations in addition to these dichotomous relationships, exposures were analyzed using average summary levels derived from probability, intensity, frequency, and job duration for all jobs prior to index pregnancy (Table 4). The matched adjusted analyses produced elevated ORs for moderate and high levels of exposures for pesticides, non-welding metals, and non-chlorinated/non-paint VOCs; of these, only non-welding metals demonstrated a consistent exposure-response pattern (p for trend = 0.08). Additionally, pesticides showed elevated ORs at the moderate and high exposure levels

when examining the full adjusted sample (OR = 1.52; 95% CI: 0.92-2.53 and OR = 1.68; 95% CI: 1.04-2.72, respectively; p for trend < 0.0001). Increasing exposure levels showed a reduction in risk of sporadic bilateral retinoblastoma for ionizing radiation, paint, and in particular chlorinated VOC exposures which showed a significant reduction in risk (OR = 0.56; 95% CI: 0.32-0.96) when the full sample was analyzed. Inconsistent trends were noted between the full and matched samples for SO2 and PAH exposures.

Exposure in year before index pregnancy

Similar to any prior exposure, exposure to pesticides and non-welding metals produced elevated ORs of 1.67 (95% CI: 0.85-3.28) and 1.22 (95% CI: 0.69-2.16), respectively, in the matched sample (Table 3). When considering the sample in full, only the risk estimate for pesticides reached statistical significance (OR = 2.12; 95% CI: 1.25-3.61). ORs below the null were seen for welding fumes, SO2, PAH, ionizing radiation, paint, chlorinated VOC, and non-chlorinated/non-paint VOC exposures. The direction of effect estimates did not differ between full and matched samples for any of the exposures except for welding fumes. The magnitude of association between these two samples differed most for pesticide exposure.

Exposure-response analyses of average summary scores based on probability, intensity, frequency, and job duration for jobs showed similar findings to those observed for jobs held ten years prior to conception (with the exception of non-chlorinated/non-paint VOCs), although some differences in the magnitude of association were noted (Table 5). In the matched adjusted sample, no association reached statistical significance. Only non-welding metals produced elevated ORs for both moderate and high exposure levels but no consistent exposure-response trend was observed (p for trend = 0.13) and results were imprecise. In contrast, exposures to PAHs and non-chlorinated/non-paint VOCs showed reduced risks for sporadic bilateral retinoblastoma at moderate and high levels with some indication of a downward exposure-response trend. ORs for other exposures were not meaningfully different from the null, lacked exposure-response trends, or were statistically imprecise.

Sensitivity analyses

Considering only jobs with an exposure probability of 50% or greater as exposed (and jobs with a lower probability as unexposed) resulted in patterns of effect estimates similar to those seen above for cumulative exposure levels but not for time-weighted average levels. That is, although time-weighted average exposure levels using this metric produced comparable results for those exposures with risk estimates below the null (ionizing radiation, paint, and chlorinated VOC), exposure-response trends using this metric no longer existed for non-welding metals (moderate: OR = 1.54, 95% CI: 0.73-3.27; high: OR = 1.36, 95% CI: 0.60-3.09). In addition, risk estimates for pesticide exposure were close to the null for all jobs prior to index pregnancy (moderate: OR = 1.07, 95% CI: 0.44-2.60; high: OR = 0.97, 95% CI: 0.39-2.44), and ORs were below the null for jobs held in the year before index pregnancy (moderate: OR = 0.47, 95% CI: 0.11-2.09; high: OR = 0.57, 95% CI: 0.10-3.27).

DISCUSSION

Although several epidemiologic studies have been reported on parental occupations and their associations with retinoblastoma risk in offspring [3,9-13,21-26], to our knowledge this is the largest study examining paternal occupational exposures and retinoblastoma in sporadic bilateral cases only. The risk of sporadic bilateral retinoblastoma was increased in relation to paternal occupational exposure to pesticides in the 10 years prior to conception as well as in the year prior to conception in the full adjusted sample but not in the matched sample, although the effect estimate remained elevated. A slightly higher risk was seen when

exposure occurred in the year prior to index pregnancy compared to any prior exposure. An increased risk was also observed for non-welding metal exposure during the 10 years prior to conception in both the full and matched sample, but ORs were not statistically significant and no elevated risks were seen for the year prior to pregnancy. An extended period of relevant exposure may lead to a higher risk of genetic mutations causing disease; if so, a consistent temporal pattern was observed for non-welding metals but not for pesticides. These results appear to be consistent with previously published studies showing increased risk of retinoblastoma in parents working in the metal industry [3,9,21] but inconsistent with increased risks in the agricultural industry [3,12,22,23,26].

Due to the possibility of subjective assignment among the raters for the overall exposure score to each agent, we also incorporated additional sources of exposure variability such as probability and frequency into our assessment. Exposure-response trends were seen more in the full sample as compared to the matched sample. In the full sample, the highest risk of bilateral retinoblastoma among fathers exposed to pesticides was found in high levels of exposure. This was not true, however, in the matched sample of all prior jobs. This pattern could be explained by highly pesticide-exposed case fathers who do not have controls and therefore are only in the full analysis. The case fathers without controls were more likely to have low SES, a group that includes some highly pesticide exposed workers such as farm workers and landscape workers. When these fathers are included in the full sample, there are not similar control fathers who might also have these highly exposed jobs. It is possible that, even with adjustment for educational level in the full sample, residual confounding led to a spuriously increased OR. For non-welding metals, increasing levels of exposure yielded elevated risks for bilateral retinoblastoma in an exposure-response fashion, which was consistent in both samples. Similarities in these effect estimates with the overall exposure scores assigned by the raters suggest accurate subjective overall risk estimates.

Contrary to studies demonstrating an increased risk of retinoblastoma [21] and brain cancer[15] in children whose fathers were welders and machinists, our findings do not show consistent risk estimates with welding fume exposures across levels and time periods before conception. These results, however, are based on small sample sizes and risk estimates were imprecise. Similarly, our findings differ from studies suggesting harmful effects of SO2 [27] and PAH [28,29] on carcinogenic outcomes in offspring.

Risk estimates below the null were seen for high levels of ionizing radiation, paint, and chlorinated VOC exposures. These results could be due to chance, particularly for ionizing radiation and paint exposures considering their low prevalence and small sample sizes in the moderate and high levels of exposure. In addition, the generally modest agreement in exposure estimates between raters suggests that exposure measurement error may have affected results, with an unpredictable direction of bias for categorical exposures [30]. The finding for radiation exposure seems particularly affected by random error and measurement error, given the definitive animal data and emerging human data on ionizing radiation as a germline mutagen [31], including data on medical radiation from the same case-control study [5].

Among all exposures assessed, non-chlorinated/non-paint VOCs were most prevalent among both cases and controls. The direction of risk estimates for any versus no exposure are conflicting in the full and matched sample of any prior exposure (above the null) compared to exposure in the year before index pregnancy (below the null). These effects remain consistent when stratified by time-weighted average levels of exposure. This finding is difficult to explain based on knowledge that negative health effects from exposure to VOCs are predicted mostly by length and level of exposure [32].

The results of this study must be interpreted by recognizing several possible limitations. First, selection bias can be a major problem when designing and interpreting case-control studies. Control group selection and factors determining participation of cases and controls play a key role in evaluating this bias. In our study, controls were matched to hospital-based cases based on birth year and were selected among friends and family of the case child. This may have introduced the possibility of overmatching for exposures that relate to socioeconomic status or geographic location, resulting in reduced power to detect associations. Furthermore, results were often different between the full unmatched and matched samples. The cases with and without controls differed in race, education level, and other factors which may have led to bias in the full unmatched analyses even with adjustment for these factors. Methodologically, matched analyses are the most appropriate, and the results from the matched sample are more likely to be accurate. In addition, we had limited ability to distinguish between exposures from the 10 years prior to conception and the year prior to conception due to moderate overlap in exposure estimates. For time-weighted average exposures, the mean Spearman correlation was 0.66 (range: 0.53 to 0.83), and for cumulative exposures, the mean Spearman correlation was 0.57 (range: 0.43 to 0.80).

Recall bias is likely to be of concern if fathers of case children are more likely to accurately report specific exposures potentially associated with the disease compared with fathers of control children. Additionally, case fathers may report more detailed job histories than do parents of control children. To assess the presence of recall bias, we compared the number of jobs reported among case and control fathers. Case fathers held an average of 3.0 jobs prior to conception while control fathers held an average of 3.1 jobs prior to conception. Similar reporting in the number of jobs among cases and controls suggest little concern for recall bias.

In conclusion, our findings suggest a potential role of paternal occupational exposures in the etiology of childhood retinoblastoma. Odds ratios below the null for some agents are difficult to explain and may be due to chance or exposure misclassification. The potentially elevated risks for non-welding metal exposure and perhaps pesticide exposure are consistent with prior literature and should be further explored in studies with a more detailed exposure assessment.

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Relevant abbreviations and definitions

CI	confidence interval
OR	odds ratio
PAH	polycyclic aromatic hydrocarbons
RB1	retinoblastoma gene
SO2	sulfur dioxide
VOC	volatile organic compounds

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- Some studies have suggested that paternal work activities, primarily in farming and in the metalworking industry, are associated with non-germline retinoblastoma.
- We examined nine specific paternal occupational exposures in relation to sporadic bilateral (germline) retinoblastoma.
- We found an increased risk for non-welding metal exposure and possibly pesticide exposure.

Table 1

Demographic characteristics of retinoblastoma cases and controls

	All cases (n = 198)	Cases in matched sample (n = 135)	Controls (n = 245)
Father's age at conception (years), mean (SD)	32.7 (6.2)	33.2 (5.8)	32.6 (5.9)
Sex of child, n (%)			
Male	97 (49.0)	63 (46.7)	122 (49.8)
Female	101 (51.0)	72 (53.3)	117 (47.8)
Missing data	0 (0.0)	0 (0.0)	6 (2.4)
Race/ ethnicity, n (%)			
Non-Hispanic white	127 (64.1)	103 (76.3)	201 (82.0)
Non-Hispanic African-American	28 (14.1)	16 (11.9)	17 (6.9)
Hispanic	26 (13.1)	10 (7.4)	18 (7.4)
Other	17 (8.6)	6 (4.4)	9 (3.7)
Smoking status, n (%)			
Never smoked	105 (53.0)	79 (58.5)	153 (62.5)
Previous smoker	25 (12.6)	20 (14.8)	38 (15.5)
Smoked in year before index pregnancy	68 (34.4)	36 (26.7)	54 (22.0)
Education level, n (%)			
No college degree	121 (61.1)	72 (53.3)	107 (43.7)
College degree or higher	76 (38.4)	62 (45.9)	138 (56.3)
Missing data	1 (0.5)	1 (0.7)	0 (0.0)
Proxy interview, n (%)			
Yes	29 (14.7)	14 (10.4)	41 (16.7)
No	169 (85.4)	121 (89.6)	204 (83.3)

Table 2

Prevalence of paternal occupational exposures among cases and controls from any job prior to index pregnancy and jobs held in the year before index pregnancy

	Any prior		Year before index pregnancy	
Exposure	**Cases, n (%)**	**Controls, n (%)**	**Cases, n (%)**	**Controls, n (%)**
Pesticides	79 (39.9)	68 (27.8)	49 (24.8)	28 (11.4)
Welding Fumes	29 (14.7)	28 (11.4)	17 (8.6)	16 (6.5)
Non-welding metals	67 (33.8)	61 (24.9)	44 (22.2)	42 (17.1)
SO2	97 (49.0)	110 (44.9)	56 (28.3)	68 (27.8)
PAH	113 (57.1)	119 (48.6)	71 (35.9)	77 (31.4)
Ionizing radiation	8 (4.0)	13 (5.3)	3 (1.5)	9 (3.7)
Paint	27 (13.6)	37 (15.1)	16 (8.1)	23 (9.4)
Chlorinated VOC	69 (34.9)	96 (39.2)	42 (21.2)	50 (20.4)
Non-chlorinated/ non-paint VOC	178 (89.9)	220 (89.8)	139 (70.2)	175 (71.4)

Table 3

Crude and adjusted ORs for sporadic bilateral retinoblastoma in relation to any versus no paternal occupational exposures from any job prior to index pregnancy and jobs held in the year before index pregnancy

	Full sample								
	Crude			Adjusted*			Matched + Adjusted**		
Exposure	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**	**OR**	**95% CI**	**P**
Any prior									
Pesticides	1.73	1.16-2.58	0.01	1.64	1.08-2.50	0.02	1.40	0.85-2.30	0.18
Welding Fumes	1.33	0.76-2.32	0.32	1.22	0.68-2.19	0.52	0.98	0.48-2.00	0.96
Non-welding metals	1.54	1.02-2.33	0.04	1.35	0.86-2.12	0.19	1.40	0.82-2.37	0.22
SO2	1.18	0.81-1.72	0.39	0.95	0.63-1.43	0.79	0.96	0.59-1.56	0.86
PAH	1.41	0.97-2.05	0.08	1.23	0.82-1.86	0.32	1.03	0.63-1.69	0.90
Ionizing radiation	0.75	0.31-1.85	0.53	0.77	0.30-1.98	0.58	0.68	0.22-2.12	0.51
Paint	0.89	0.52-1.52	0.66	0.73	0.41-1.29	0.27	0.64	0.33-1.26	0.20
Chlorinated VOC	0.83	0.56-1.23	0.35	0.70	0.46-1.07	0.10	0.74	0.44-1.23	0.25
Non-chlorinated/ non-paint VOC	1.01	0.54-1.88	0.97	1.11	0.56-2.21	0.76	1.52	0.69-3.36	0.30
Year before index pregnancy									
Pesticides	2.55	1.53-4.24	<0.001	2.12	1.25-3.61	0.01	1.67	0.85-3.28	0.14
Welding Fumes	1.34	0.66-2.73	0.41	1.19	0.57-2.49	0.65	0.94	0.39-2.23	0.88
Non-welding metals	1.38	0.86-2.21	0.18	1.18	0.71-1.96	0.51	1.22	0.69-2.16	0.50
SO2	1.03	0.68-1.56	0.90	0.79	0.50-1.26	0.32	0.74	0.44-1.26	0.27
PAH	1.22	0.82-1.81	0.33	0.97	0.62-1.51	0.87	0.81	0.48-1.40	0.45
Ionizing radiation	0.40	0.11-1.51	0.18	0.46	0.12-1.82	0.27	0.46	0.09-2.23	0.33
Paint	0.85	0.44-1.65	0.63	0.73	0.36-1.47	0.38	0.73	0.32-1.64	0.44
Chlorinated VOC	1.05	0.66-1.67	0.84	0.90	0.55-1.46	0.66	0.90	0.51-1.59	0.71
Non-chlorinated/ non-paint VOC	0.94	0.62-1.42	0.78	0.87	0.56-1.35	0.53	0.77	0.47-1.27	0.30

*Adjusted for fathers' smoking status, race, education, age, proxy status, and birth year of child.

**Matched sample used; matched on child's age group with additional adjustments for fathers' smoking status, race, education, age, and proxy status.

Table 4

Crude and adjusted ORs for sporadic bilateral retinoblastoma in relation to time-weighted average levels of paternal occupational exposures from *all jobs prior to index pregnancy*

	Full sample					Matched sample				
		Crude		Adjusted*			Crude		Adjusted**	
Exposure level	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**
Pesticides										
None/ Low	183 [1]	1.00 (ref)		1.00 (ref)		165 [1]	1.00 (ref)		1.00 (ref)	
Moderate	125 [>1-1.5]	1.20	0.76-1.90	1.52	0.92-2.53	107 [>1-1.4]	1.28	0.77-2.12	1.40	0.77-2.54
High	135 [>1.5-27]	1.74	1.11-2.74	1.68	1.04-2.72	108 [>1.4-27]	1.21	0.73-2.01	1.13	0.64-1.98
Welding fumes										
None/ Low	386 [1]	1.00 (ref)		1.00 (ref)		335 [1]	1.00 (ref)		1.00 (ref)	
Moderate	28 [>1-3.1]	1.11	0.52-2.40	1.08	0.48-2.42	22 [>1-3.3]	0.69	0.26-1.81	0.68	0.25-1.85
High	29 [3.1-27]	1.58	0.74-3.38	1.36	0.62-3.01	23 [>3.3-27]	1.69	0.72-3.94	1.37	0.54-3.47
Non-welding metals										
None/ Low	315 [1]	1.00 (ref)		1.00 (ref)		271 [1]	1.00 (ref)		1.00 (ref)	
Moderate	65 [>1-3.4]	1.28	0.75-2.19	1.15	0.64-2.04	54 [>1-3.4]	1.24	0.68-2.29	1.09	0.53-2.22
High	63 [>3.4-27]	1.87	1.08-3.24	1.61	0.90-2.87	55 [>3.4-27]	2.19	1.22-3.94	1.74	0.89-3.43
SO2										
None/ Low	235 [1]	1.00 (ref)		1.00 (ref)		204 [1]	1.00 (ref)		1.00 (ref)	
Moderate	108 [>1-3.4]	1.21	0.76-1.91	1.07	0.66-1.76	85 [>1-3.4]	1.30	0.77-2.20	1.24	0.68-2.26
High	100 [>3.4-27]	1.20	0.75-1.92	0.85	0.50-1.44	91 [>3.4-27]	1.06	0.63-1.78	0.78	0.43-1.41
PAH										
None/ Low	210 [1]	1.00 (ref)		1.00 (ref)		189 [1]	1.00 (ref)		1.00 (ref)	
Moderate	117 [>1-3.6]	1.38	0.87-2.17	1.40	0.86-2.27	95 [>1-3.5]	1.22	0.73-2.04	1.20	0.68-2.12
High	116 [>3.6-27]	1.50	0.95-2.37	1.12	0.67-1.86	96 [>3.5-27]	1.20	0.72-2.00	0.89	0.48-1.66
Ionizing radiation										
None/ Low	422 [1]	1.00 (ref)		1.00 (ref)		362 [1]	1.00 (ref)		1.00 (ref)	
Moderate	11 [>1-3.2]	1.02	0.31-3.39	1.09	0.32-3.74	9 [>1-2.9]	0.89	0.22-3.63	0.81	0.19-3.54
High	10 [>3.2-27]	0.52	0.13-2.05	0.49	0.11-2.11	9 [>2.9-27]	0.51	0.10-2.49	0.56	0.11-2.88
Paint										

	Full sample					Matched sample				
		Crude		Adjusted*			Crude		Adjusted**	
Exposure level	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**
None/ Low	379 [1]	1.00 (ref)		1.00 (ref)		327 [1]	1.00 (ref)		1.00 (ref)	
Moderate	32 [>1-4.0]	1.22	0.59-2.50	1.02	0.48-2.19	26 [>1-4.0]	0.93	0.40-2.14	0.87	0.36-2.09
High	32 [>4.0-27]	0.64	0.30-1.36	0.51	0.23-1.12	27 [>4.0-27]	0.61	0.25-1.49	0.46	0.18-1.21
Chlorinated VOC										
None/ Low	278 [1]	1.00 (ref)		1.00 (ref)		237 [1]	1.00 (ref)		1.00 (ref)	
Moderate	83 [>1-2.7]	1.02	0.63-1.67	0.88	0.52-1.49	71 [>1-2.8]	0.92	0.53-1.60	0.86	0.45-1.62
High	82 [>2.7-27]	0.67	0.40-1.11	0.56	0.32-0.96	72 [>2.8-27]	0.75	0.42-1.31	0.65	0.35-1.22
Non-chlorinated/ non-paint VOC										
None/ Low	46 [1]	1.00 (ref)		1.00 (ref)		38 [1]	1.00 (ref)		1.00 (ref)	
Moderate	198 [>1-4.0]	1.07	0.56-2.05	1.34	0.65-2.76	171 [>1-3.7]	1.47	0.68-3.16	2.20	0.92-5.26
High	199 [>4.0-27]	1.27	0.66-2.44	1.30	0.64-2.66	171 [>3.7-27]	1.33	0.62-2.86	1.45	0.61-3.44

*Adjusted for father's smoking status, race, education, age, proxy status, and birth year of child.

**Matched on child's age group, with additional adjustments for father's smoking status, race, education, age, and proxy status.

Table 5

Crude and adjusted ORs for sporadic bilateral retinoblastoma in relation to time-weighted average levels of paternal occupational exposures from *jobs held in the year before index pregnancy*

	Full sample					Matched sample				
		Crude		Adjusted*			Crude		Adjusted**	
Exposure level	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**
Pesticides										
None/ Low	305 [1]	1.00 (ref)		1.00 (ref)		274 [1]	1.00 (ref)		1.00 (ref)	
Moderate	69 [>1-2.0]	1.16	0.69-1.96	1.15	0.67-1.98	57 [>1-1.5]	1.02	0.56-1.85	0.81	0.43-1.53
High	69 [>2.0-27]	2.08	1.22-3.54	1.64	0.94-2.86	49 [>1.5-27]	1.30	0.70-2.42	1.15	0.56-2.37
Welding fumes										
None/ Low	410 [1]	1.00 (ref)		1.00 (ref)		354 [1]	1.00 (ref)		1.00 (ref)	
Moderate	18 [>1-5.0]	1.58	0.61-4.09	1.51	0.56-4.05	13 [>1-5.0]	1.15	0.37-3.57	1.07	0.33-3.51
High	14 [>5.0-27]	1.11	0.39-3.11	0.90	0.31-2.61	13 [>5.0-27]	1.15	0.37-3.57	0.81	0.24-2.72
Non-welding metals										
None/ Low	356 [1]	1.00 (ref)		1.00 (ref)		305 [1]	1.00 (ref)		1.00 (ref)	
Moderate	42 [>1-4.7]	1.33	0.70-2.52	1.14	0.58-2.24	38 [>1-5.5]	1.61	0.81-3.19	1.26	0.59-2.71
High	45 [>4.7-27]	1.52	0.81-2.83	1.32	0.68-2.54	37 [>5.5-27]	1.52	0.76-3.03	1.27	0.58-2.79
SO2										
None/ Low	314 [1]	1.00 (ref)		1.00 (ref)		271 [1]	1.00 (ref)		1.00 (ref)	
Moderate	54 [>1-5.9]	1.15	0.65-2.06	0.96	0.51-1.78	46 [>1-5.9]	1.15	0.61-2.19	1.00	0.49-2.03
High	75 [>5.9-27]	0.93	0.56-1.54	0.65	0.37-1.14	63 [>5.9-27]	0.83	0.46-1.50	0.58	0.30-1.13
PAH										
None/ Low	289 [1]	1.00 (ref)		1.00 (ref)		254 [1]	1.00 (ref)		1.00 (ref)	
Moderate	81 [>1-6.1]	1.41	0.86-2.32	1.14	0.66-1.96	67 [>1-6.1]	1.31	0.76-2.27	0.96	0.52-1.79
High	73 [>6.1-27]	0.97	0.58-1.63	0.71	0.40-1.26	59 [>6.1-27]	0.74	0.40-1.37	0.59	0.30-1.18
Ionizing radiation										
None/ Low	431 [1]	1.00 (ref)		1.00 (ref)		369 [1]	1.00 (ref)		1.00 (ref)	
Moderate	6 [>1-7.0]	0.61	0.11-3.34	0.63	0.10-3.98	6 [>1-7.0]	0.89	0.16-4.91	1.26	0.22-7.29
High	6 [>7.0-27]	0.24	0.03-2.09	0.31	0.04-2.75	5 [>7.0-27]	<0.00	0.00->99	<0.00	0.00->99
Paint										

	Full sample					Matched sample				
		Crude		Adjusted*			Crude		Adjusted**	
Exposure level	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**	**N [Score]**	**OR**	**95% CI**	**OR**	**95% CI**
None/ Low	404 [1]	1.00 (ref)		1.00 (ref)		347 [1]	1.00 (ref)		1.00 (ref)	
Moderate	18 [>1-7.0]	1.92	0.73-5.05	1.99	0.73-5.41	18 [>1-8.5]	1.13	0.43-2.99	1.32	0.48-3.68
High	21 [>7.0-27]	0.38	0.14-1.06	0.27	0.09-0.78	15 [>8.5-27]	0.44	0.12-1.60	0.32	0.08-1.24
Chlorinated VOC										
None/ Low	349 [1]	1.00 (ref)		1.00 (ref)		301 [1]	1.00 (ref)		1.00 (ref)	
Moderate	48 [>1-5.0]	1.24	0.68-2.26	1.07	0.57-2.01	40 [>1-5.0]	1.19	0.61-2.34	1.09	0.55-2.17
High	46 [>5.0-27]	0.80	0.42-1.49	0.66	0.34-1.29	39 [>5.0-27]	0.70	0.34-1.47	0.57	0.25-1.33
Non-chlorinated/ non-paint VOC										
None/ Low	126 [1]	1.00 (ref)		1.00 (ref)		111 [1]	1.00 (ref)		1.00 (ref)	
Moderate	151 [>1-4.3]	0.86	0.54-1.39	0.90	0.54-1.47	134 [>1-4.3]	0.85	0.51-1.44	0.85	0.48-1.52
High	166 [>4.3-27]	0.99	0.62-1.58	0.80	0.48-1.32	135 [>4.3-27]	0.79	0.47-1.33	0.69	0.39-1.23

*Adjusted for father's smoking status, race, education, age, proxy status, and birth year of child.

**Matched on child's age group, with additional adjustments for father's smoking status, race, education, age, and proxy status.

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