HHS Public Access

Author manuscript

Am J Ophthalmol. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Am J Ophthalmol. 2017 April ; 176: 166–173. doi:10.1016/j.ajo.2017.01.016.

Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group

Negar Omidakhsh[1], **Arupa Ganguly**[2], **Greta R. Bunin**[3], **Ondine S. von Ehrenstein**[4], **Beate Ritz**[1], and **Julia E. Heck**[1,*]

[1]Department of Epidemiology, Fielding School of Public Health, University of California, 650 Charles E Young Dr., Box 951772, Los Angeles, CA 90095-1772 USA

[2]Department of Genetics, University of Pennsylvania, Philadelphia, Pennsylvania, USA415 Anatomy Chemistry Building, 3620 Hamilton Walk Philadelphia, PA 19104

[3]Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, 3535 Market Street, Room 1472, Philadelphia, PA 19104

[4]Department of Community Health Sciences, Fielding School of Public Health, University of California, 650 Charles E Young Dr., Box 951772, Los Angeles, CA 90095-1772 USA

Abstract

Purpose—To examine whether parental pesticide exposure contributes to the development of sporadic retinoblastoma.

Design—Case-control study.

Methods—Data were collected by a large multicenter study of sporadic retinoblastoma in which parents of 99 unilateral and 56 bilateral age matched case-control pairs were interviewed by telephone. Retrospective exposure information was collected on the type, location, timing and frequency of residential pesticide use. We used conditional logistic regression analyses to estimate odds ratios for maternal pesticide exposure in the month before or during pregnancy and to assess whether the type of product, and the circumstances under which it was applied, were associated with risk of disease.

Results—Unilateral retinoblastoma was associated with parental insecticide use (OR, 2.8; CI, 1.1–6.7) and the use of professional lawn or landscape services (OR, 2.8; CI, 1.0–8.2). For bilateral disease we observed large point estimates for several exposures but the small number of cases rendered these results uninformative i.e. resulted in wide confidence intervals. Whether parents used the pesticide inside vs. outside the home did not appear to modify risk estimates for unilateral retinoblastoma (OR, 2.5; CI, 0.9–7.0 vs. OR, 2.5; CI, 1.0–6.5), nor did the type,

*Corresponding Author: Dr. Julia E Heck, UCLA Department of Epidemiology, 650 Charles E Young Drive, Box 951772, Los Angeles, CA, 90095-1772, USA, Phone: 310-825-4254, Fax: 310-206-6039, jeheck@ucla.edu.

frequency, timing related to pregnancy or applicator of pesticide used influence estimates to an appreciable degree for disease.

Conclusions—Our results suggest that parental pesticide exposure before or during pregnancy may play a role in the development of childhood retinoblastoma. Retrospectively collected exposure data introduces the possibility of recall bias, therefore, results should be interpreted cautiously until additional studies are conducted.

Introduction

Retinoblastoma is a malignant tumor of the retina that occurs due to mutation or loss of both alleles of the *RB1* gene. It is an embryonal tumor most commonly found in young children[1] with a majority (63%) being diagnosed before age 2, and 95% by age 5. In hereditary retinoblastoma (6–10% of cases), a germline mutation of the *RB1* gene is inherited from a parent, and most of these cases present bilaterally. In 30% of cases, a *de novo* germline mutation occurs in parental germline cells (most frequently from the father)[2] or occurs in very early embryonic development ("sporadic heritable retinoblastoma"); these cases also tend to present as bilateral disease. In the remaining cases, two somatic mutations occur in the same retinal cell during pregnancy or early life, and these cases present unilaterally ("nonheritable retinoblastoma").

Though the 10-year survival rate is high in the United States (93%), these rates vary considerably in low to middle income countries (40%–79%, respectively).[3] Despite the high cure rates, retinoblastoma survivors tend to have a poorer quality of life and have greater school absenteeism.[4] Further, pediatric cases of heritable retinoblastoma have an elevated risk for developing sarcoma and leukemia by age 14.[5] In adulthood, these children have an increased risk of chronic medical conditions including a second malignant neoplasm.[6]

There has been some evidence suggesting a role for occupational or environmental exposures in retinoblastoma development. Retinoblastoma has been related to residential exposure to air pollution,[7–9] parental occupational exposure to oil mists[10] and to parental employment in radio or television repair[11], shoe or leather work[12], electrical work,[12] or in the metal industry.[13, 14] Although the literature has shown fairly consistent associations between the home use of insecticides or herbicides and other childhood cancer types,[15, 16] thus far, findings on retinoblastoma have been equivocal. Parental employment as a pesticide applicator[17] or in horticultural, forestry or farm work[18–20] has been associated with a null or even weakly decreased risk for "childhood eye cancer" (all types combined) or retinoblastoma in previous studies, with the exception of the Agricultural Health Study that reported a higher risk (SIR,1.63; CI, 0.41–6.53) with wide confidence intervals.[21] Only one study[22] found parental employment-related pesticide exposure to be associated with offspring bilateral retinoblastoma (OR, 2.12; CI, 1.25–3.61). For unilateral disease, increased risk was observed among children whose maternal grandfathers were farmers (OR, 10.0; CI, 1.4–433).[14] With the exception of the latter two studies that observed positive associations,[14, 22] none of the others excluded familial cases, nor did they estimate risks separately for non-heritable and heritable disease. Only one previous study investigated the use of home insect or garden sprays, and suggested increases in risk for non-heritable

retinoblastoma, but the sample size was very small and the estimates accordingly imprecise (OR, 2.7; CI, 0.6–15.6).[23] The purpose of the present study was to conduct an in-depth examination of associations between sporadic retinoblastoma and pesticide exposures.

Methods

For our case-control study, ethics approval was obtained prospectively through the Institutional Review Board (IRB) of the University of Pennsylvania, the Wills Eye Institute and every participating Children's Oncology Group (COG) institution prior to subject recruitment. The abovementioned review boards approved the prospective collection of data from subjects through telephone interviews. For the retrospective data analyses of the present study, IRB approval was also obtained from the University of California, Los Angeles prior to receiving the de-identified dataset. All subjects provided verbal and/or written informed consent prior to study participation and all acts complied with HIPAA regulations.

The data for this study was collected as part of a large multi-center case-control study of retinoblastoma, which has been described in detail elsewhere.[24, 25] In brief, eligible incident cases were diagnosed with sporadic retinoblastoma on or after July 1st, 2006 through June 30, 2011 and were diagnosed and/or treated at a COG institution or at the Wills Eye Institute in Philadelphia, PA, USA. Cases were eligible if they were residing in the U.S. or Canada, had access to a home or cellular telephone, and had at least one biological parent who spoke English or Spanish that was available for participation. Children who were adopted or in foster care were excluded from participation in the present study. In total, 282 cases (186 unilateral and 96 bilateral) were recruited and completed phone interviews.

Case families were asked to nominate one or more friends or non-biological relatives with a child in the same age range as the index child (0–1, 2–3, 4–5, 6–7, 8–9, 10–11, 12–13 or 14–15 years) as potential controls. For bilateral retinoblastoma, paternal exposures are of primary interest; therefore, the "ideal control" was a child in the same age range whose father was not biologically related to the case child's father. For unilateral retinoblastoma, maternal exposures are of greatest interest; therefore, the "ideal control" was a child in the same age range whose mother was not biologically related to the case child's mother. The study attempted to contact and recruit control families starting with the child closest in age to the matched case, and moving on to the next on the list if that child was unavailable, until all potential controls had been exhausted. Only maternal questionnaires asked about home pesticide use. Four participants (2 controls, 1 unilateral case and 1 bilateral case) did not answer questions on home pesticide use and were therefore excluded from the present analyses.

Structured telephone interviews were conducted with parents of cases and controls. In addition to information on demographics and health behaviors during the perinatal period, mothers were asked detailed questions regarding residential pesticide use before conception and during pregnancy, including the use of professional lawn or landscape services; the use of pest control professionals or exterminators for their home; in-home use of insect or rodent killers; indoor foggers; home or garden use of herbicides, mold removal products, anti-

fungals, or weed killers; insect repellant; head lice treatment on the children; and for pets, the use of flea collars, flea or tick shampoos.

When parents indicated that they had applied a product themselves around their home or garden, they were asked to identify the name of the product. Depending on the question asked, between 1–43% of parents were able to identify the type of product used, and among those, parents were able to supply the name for approximately 70% of products. A large variety of products were listed by parents; therefore, we were unable to estimate effects by the specific pesticide or active ingredient used.

We estimated odds ratios (ORs) and 95% confidence intervals using conditional logistic regression for the matched pair design. Selection of variables for adjustment was based upon literature review as well as associations observed in our data.[23, 25–29] In analyses involving unilateral cases we adjusted for mother's race (White non-Hispanic, Hispanic, Other), mother's employment status (Yes/No), whether the father was living at home at the start of pregnancy (Yes/No), and the mother's age (<29, 30–34, 35+). In analyses of bilateral retinoblastoma, we adjusted for the same variables with the addition of father's age (<29, 30–34, 35+). Marital status, mother's educational attainment, maternal tobacco smoking, interview by proxy and the child's gender did not change the estimate more than 10% and therefore we did not include these variables in the final model. We conducted sensitivity analyses examining results when proxy respondents were excluded, as well as when non-ideal controls were excluded.

Results

Not all cases had a matched control; therefore, analyses were conducted on 99 matched pairs of unilateral cases/maternal controls and on 56 bilateral cases/maternal controls who completed the interview. Although efforts were made to primarily recruit age-matched children who were not biological relatives, in some instances the study accepted controls who were either unmatched or who were biological relatives (7.8% of controls). In unilateral analyses, 2% of maternal-case and 5% of maternal-control interviews were conducted with a proxy respondent, typically the other parent. No bilateral interviews were conducted with a proxy respondent.

The demographics of participants are shown in Table 1. The unilateral case group included a larger proportion of Hispanic mothers and the bilateral case group included a greater proportion of mothers with a high school education or less. Both case groups had lower family income than the control group. A total of 256 participants (82%) in our matched analyses reported ever use of any pesticide in the month before or during pregnancy.

Table 2 shows associations between residential pesticide exposure in the month before or during pregnancy and unilateral retinoblastoma. We found that the use of a product to kill insects or diseases on the lawn was associated with the development of unilateral retinoblastoma (OR, 2.8; CI, 1.1–6.7). Using professional lawn or landscaping services was also associated with increased risk of unilateral disease (OR, 2.8; CI, 1.0–8.2). Home use of

weed killer was associated with unilateral retinoblastoma development (OR, 2.3; CI, 0.9–5.4) but the 95% CI was wide and included the null.

Table 3 summarizes associations between maternal residential pesticide exposure in the month before or during pregnancy and bilateral retinoblastoma. High positive point estimates with wide confidence intervals that included the null were estimated for use of professional lawn or landscape services (OR, 3.4; CI, 0.6–18.0). Although for several of the other measures effect estimates were also elevated above 1, our point estimates were similarly imprecise due to the small number of cases.

Table 4 shows multivariate analyses with more detailed information on the type of product, and the circumstances under which it was applied, utilizing the same types of exposures as shown in the previous tables. In general, the effect estimates for retinoblastoma were similar for the various types, locations, timing and frequency of pesticide use, with overlapping confidence intervals; i.e. risk of unilateral and bilateral retinoblastoma increased regardless of whether families had used sprays or other types of products; whether they used the product inside or outside the home; and whether they used them early or late in pregnancy.

About half of participants reported a product name for which ingredients could be identified, of which many included combinations of pyrethroides or neonicotinamides (e.g. imidocloprid). Other reported products used for weed control included glyphosate, 2,4-D, 2-methyl-4-chlorophenoxyacetic acid (MCPA), and dicamba. Sensitivity analyses excluding proxy respondents and non-ideal controls yielded effect estimates similar to those reported here (data not shown).

Discussion

In our case-control study which stratified by laterality of disease, we observed positive associations for some prenatal pesticide use and child sporadic retinoblastoma. For unilateral retinoblastoma, odds ratios were increased more than 2-fold with reported use of professional lawn or landscaping services, and similarly with use of insecticides inside or outside the home. Use of weed and insect control products on the lawn also resulted in increased odds ratios, however the confidence intervals included the null. While there also was some suggestion of increased risks in relation to these exposures for bilateral cases, all point estimates were estimated relatively imprecisely due to the small number of cases. Our findings for unilateral cases are consistent with the proposed underlying mechanisms of disease, which suggests that unilateral retinoblastoma is likely associated with somatic mutations during fetal development. Given the present study tests many potential associations, issues of multiple comparison are a concern; however, as most point estimates for pesticide use and retinoblastoma were in the direction of a positive association, we believe our study provides evidence which is suggestive of a true association.

In this study, questions on pesticide use were asked only of the mother, and mothers may not have been aware of all pesticides that were applied by the father in or around the home. If pesticide applications contributed to do novo mutations in paternal germline cells, leading to bilateral disease, we were not able to address these exposures. However, the separation of

exposures is not easy to make if both parents are living together and we assume if one reported using the pesticide the other parent is likely exposed as well.

Since retinoblastoma in children is a rare disease with an estimated mean age-adjusted incidence in the USA of 11.8 per million children aged 0–4 years (95% CI 10.9 to 12.8) from 1975 to 2004,[30] studies investigating environmental risk factors are limited and most have thus far not distinguished between unilateral and bilateral cases, nor focused only on sporadic cases. The increased risks we see for different types of residential pesticide applications during pregnancy and unilateral cases are corroborated by the only other study of retinoblastoma reporting on the use of home insect or garden sprays.[23] This study estimated a similarly increased point estimate for non-heritable unilateral retinoblastoma, although the confidence intervals were wide (OR, 2.7; CI, 0.6–15.6).[23] Several other studies examined occupational pesticide exposures. One such study which assessed paternal occupational exposure based on a job exposure matrix applied to jobs 10 year prior to conception reported an increased odds ratio for non-familial bilateral retinoblastoma of 1.40 (95% CI: 0.85–2.30).[13] Other occupational studies assessed parental pesticide exposure more crudely, including working as a pesticide applicator,[17] horticultural, forestry or farm work[18–20] and child retinoblastoma (or all childhood “eye cancer”, of which retinoblastoma accounts for over 90% of cases) reporting no or even somewhat decreased risks. However, these studies were flawed in that they either obtained all occupational data from birth records and thus did not have access to information such as specific agents exposed to at work, employment dates or number of jobs held, or they made so many comparisons that any or all of the findings could have occurred by chance. The great majority of these studies used data linkage techniques to obtain cancer diagnoses based upon participant address at one time period such as birth, which would exclude subjects who migrated, potentially misclassifying the results.[17, 18, 20, 21] The Agricultural Health Study cohort identified 50 incident cases of various child cancers but only 2 retinoblastomas, thus the reported 60% increased risk for parental pesticide exposures had wide CI for this cancer and has to be interpreted cautiously.[21] Notably, the above studies mixed familial bilateral and unilateral cases and thus the findings are not directly comparable to ours. Our own study of air toxins based on ambient monitoring data suggested increases in unilateral retinoblastoma related to several volatile chemicals such as xylenes and toluene[9] which supports the notion that environmental toxins act as risk factors during pregnancy and contribute to the etiology of sporadic retinoblastoma in children.

Studies examining associations between pesticide use and childhood cancer so far have mostly focused on leukemia. Two recent systematic reviews/meta-analyses involving 13 and 15 studies, respectively, estimated positive associations between childhood leukemia and prenatal residential pesticide exposures in the pooled analyses.[15, 31] Studies on pesticides and other child cancers are much rarer. The embryonal central nervous system (CNS) tumors, and the sympathetic nervous system tumors such as neuroblastoma, share with retinoblastomas a common origin in the germinal neuroectodermal layer.[1, 32] A relatively large recent study from 10 pediatric oncology centers in Australia found associations between childhood CNS cancer and preconception and early pregnancy exposure to home treatment with pesticides, and paternal occupational pesticide exposure.[33] However a meta-analysis of neuroblastoma and paternal occupational exposure based on seven case-control

and two cohort studies did not report positive associations.[34] Overall, there is a growing body of evidence that prenatal or preconceptional pesticide exposure contributes to some childhood cancers, including those of developmental origin.

While we do not have a record of actual types of pesticides used by professional landscapers, an exposure type related to increased risk in our study, it is likely that such services typically use herbicides applied widely around the home. In 2007, the most commonly applied pesticides in US homes and gardens were 2,4-D, glyphosate, carbaryl, mecoprop (MCPP), and pendimethalin.[35] Also related to increased risk in our study was the use of a "Product to kill insects or diseases inside or outside the home, such as Raid". Home use products frequently contain mixtures of two or more active substances. While we were unable to examine specific types or classes of pesticides, most subjects who used home pesticides were likely exposed to more than one toxic agent during sensitive developmental periods, and further research is needed to identify whether and how the mixture of these substances may be involved in the development of retinoblastoma.

Previous studies have described retinoblastoma incidence with one post-conception hit for bilateral cases and two such hits for unilateral cases.[36] Children who inherit one defective copy of the *RB1* gene have an increased susceptibility to develop retinoblastoma through inactivation of the second allele (approximately 90%).[37] It is suggested that the *RB1* gene inactivation occurs during DNA replication in proliferating retinal progenitor cells and retinal progenitor cell proliferation occurs only in the fetal retina.[38, 39] Although genetic alterations to both copies of the *RB1* gene have been shown to be necessary to induce retinoblastoma it is still unclear which type and location of mutational events may be required for tumorigenesis.[40] Thus, this etiology is consistent with elevated risks we estimated related to prenatal pesticide exposure for unilateral cases acting as a 'second hit'. Overall our findings for use of pesticides and unilateral vs. bilateral retinoblastoma in children are consistent with the underlying postulated etiology.

Friend controls are likely to have been more similar to cases on many factors that relate to socioeconomic status including race and income. A previous study by our group observed a greater number of concordant case-control sets than would be randomly expected for demographic characteristics such as race/ethnicity, education, income and paternal age.[41] However, this relationship was not observed when reviewing potential exposures of interest, suggesting that utilizing friend controls may not have resulted in overmatching for several exposures, although it likely provides cases and controls that are more closely matched on possible covariates, reducing confounding. To further mitigate the effects of confounding bias due to maternal race, we adjusted for this in all of our models.

While for this very rare childhood cancer ours was a large study, the numbers in the different categories are small, which is a limitation of the study and may lead to unstable estimates. An additional limitation of our study is the possibility of recall errors. In retrospective studies in which mothers are asked about environmental exposures during or prior to pregnancy it is possible that case mothers over-report exposures or that control mothers under-report exposures.[42] Yet the reported frequency of pesticide use was similar to those reported elsewhere,[35] particularly studies asking about prenatal or early childhood

application frequency.[43] The study design did not allow for the collection of biological samples or water tests to examine the presence of chemical metabolites in mothers or children. Ideally, we would like to gather prospective data on pesticide use and other potential risk factors, along with toxicological samples, at multiple time points within a cohort study; however, for rare diseases such as retinoblastoma in children, this design is not feasible.

In conclusion, the observed increase in unilateral retinoblastoma associated with prenatal pesticide use around the home during pregnancy and the suggestion of several pesticide exposures contributing to bilateral cases adds to the body of evidence that suggests that pesticide use during critical prenatal or preconceptional time periods increases risks for these rare childhood cancers. There are few case-control studies on retinoblastoma to date worldwide, and our results require replication in other populations. More detailed information on types of pesticides in the home and from other sources such as diets would be desirable in future studies. Although retinoblastoma is a very rare disease, for affected individuals and families the implications are devastating, thus it is important to identify preventable risk factors. Our findings indicate that there is a need to raise awareness of the implications of home use of pesticides during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

A. This work was supported in part by grants from the National Institute of Health (NIH) in the United States, the National Cancer Institute (NCI) in the United States, and the National Institute of Environmental Health Sciences (NIEHS) in the United States. Specific grants are NIH/NCI (RO1 - CA118580), NIH/NIEHS (R03ES021643, R21ES019986), and ARRA supplement in California, U.S.A. (CA-118580-03S1). Mrs. Omidakhsh was supported by the Research Training Program of the Southern California NIOSH Education and Research Center (Grant Agreement Number T42OH008412) from the Centers for Disease Control and Prevention (CDC) and a grant from the Jonsson Cancer Center Foundation/UCLA in California, U.S.A. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

B. No author of the present study has any financial disclosures.

C. The authors thank Mr. Andrew Park for his assistance in developing the original code for this manuscript and Ms. Stephanie Ly for compiling the names and active ingredients of pesticides reported by mothers in this study. Both contributors are affiliated with the University of California, Los Angeles.

References

1. Gatta G, Ferrari A, Stiller CA, et al. Embryonal cancers in Europe. Eur J Cancer. 2012; 48:1425–33. [PubMed: 22357215]
2. Kato MV, Ishizaki K, Shimizu T, et al. Parental origin of germ-line and somatic mutations in the retinoblastoma gene. Hum Genet. 1994; 94:31–8. [PubMed: 8034292]
3. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol. 2010; 94:1432–6. [PubMed: 20733021]
4. Batra A, Kumari M, Paul R, Patekar M, Dhawan D, Bakhshi S. Quality of Life Assessment in Retinoblastoma: A Cross-Sectional Study of 122 Survivors from India. Pediatr Blood Cancer. 2016; 63:313–7. [PubMed: 26488435]

5. Temming P, Viehmann A, Arendt M, et al. Pediatric second primary malignancies after retinoblastoma treatment. Pediatr Blood Cancer. 2015; 62:1799–804. [PubMed: 25970657]
6. Friedman DN, Chou JF, Oeffinger KC, et al. Chronic medical conditions in adult survivors of retinoblastoma: Results of the Retinoblastoma Survivor Study. Cancer. 2016; 122:773–81. [PubMed: 26755259]
7. Ghosh JK, Heck JE, Cockburn M, Su J, Jerrett M, Ritz B. Prenatal Exposure to Traffic-related Air Pollution and Risk of Early Childhood Cancers. Am J Epidemiol. 2013; 178:1233–9. [PubMed: 23989198]
8. Heck JE, Wu J, Lombardi C, et al. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect. 2013; 121:1385–91. [PubMed: 24021746]
9. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol. 2015; 25:182–6. [PubMed: 24280682]
10. MacCarthy A, Bunch KJ, Fear NT, King JC, Vincent TJ, Murphy MF. Paternal occupation and retinoblastoma: a case-control study based on data for Great Britain 1962–1999. Occup Environ Med. 2009; 66:644–9. [PubMed: 19770353]
11. Hicks N, Zack M, Caldwell GG, Fernbach DJ, Falletta JM. Childhood cancer and occupational radiation exposure in parents. Cancer. 1984; 53:1637–43. [PubMed: 6321012]
12. Mutanen P, Hemminki K. Childhood cancer and parental occupation in the Swedish Family-Cancer Database. J Occup Environ Med. 2001; 43:952–8. [PubMed: 11725335]
13. Abdolahi A, van Wijngaarden E, McClean MD, et al. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. Occup Environ Med. 2013
14. Bunin GR, Petrakova A, Meadows AT, et al. Occupations of parents of children with retinoblastoma: a report from the Children's Cancer Study Group. Cancer Res. 1990; 50:7129–33. [PubMed: 2224847]
15. Turner MC, Wigle DT, Krewski D. Residential pesticides and childhood leukemia: a systematic review and meta-analysis. Environ Health Perspect. 2010; 118:33–41. [PubMed: 20056585]
16. Nasterlack M. Do pesticides cause childhood cancer? Int Arch Occup Environ Health. 2006; 79:536–44. [PubMed: 16463063]
17. Rodvall Y, Dich J, Wiklund K. Cancer risk in offspring of male pesticide applicators in agriculture in Sweden. Occup Environ Med. 2003; 60:798–801. [PubMed: 14504372]
18. Kristensen P, Andersen A, Irgens LM, Bye AS, Sundheim L. Cancer in offspring of parents engaged in agricultural activities in Norway. Int J Cancer. 1996; 65:39–50. [PubMed: 8543394]
19. Pearce MS, Hammal DM, Dorak MT, McNally RJ, Parker L. Paternal occupational exposure to pesticides or herbicides as risk factors for cancer in children and young adults: a case-control study from the North of England. Arch Environ Occup Health. 2006; 61:138–44. [PubMed: 17672356]
20. Fear NT, Roman E, Reeves G, Pannett B. Childhood cancer and paternal employment in agriculture. Br J Cancer. 1998; 77:825–9. [PubMed: 9514065]
21. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. Environ Health Perspect. 2004; 112:631–5. [PubMed: 15064173]
22. Abdolahi A, van Wijngaarden E, McClean MD, et al. A case-control study of paternal occupational exposures and the risk of childhood sporadic bilateral retinoblastoma. Occup Environ Med. 2013; 70:372–9. [PubMed: 23503471]
23. Bunin GR, Meadows AT, Emanuel BS, Buckley JD, Woods WG, Hammond GD. Pre- and postconception factors associated with sporadic heritable and nonheritable retinoblastoma. Cancer Res. 1989; 49:5730–5. [PubMed: 2790788]
24. Lombardi C, Ganguly A, Bunin GR, et al. Maternal diet during pregnancy and unilateral retinoblastoma. Cancer Causes Control. 2015; 26:387–97. [PubMed: 25542139]
25. Azary S, Ganguly A, Bunin GR, et al. Sporadic Retinoblastoma and Parental Smoking and Alcohol Consumption before and after Conception: A Report from the Children's Oncology Group. PloS one. 2016; 11:e0151728. [PubMed: 26991078]
26. Heck JE, Park AS, Contreras ZA, et al. Risk of Childhood Cancer by Maternal Birthplace: A Test of the Hispanic Paradox. JAMA pediatrics. 2016; 170:585–92. [PubMed: 27110958]

27. Heck JE, Contreras ZA, Park AS, Davidson TB, Cockburn M, Ritz B. Smoking in pregnancy and risk of cancer among young children: A population-based study. Int J Cancer. 2016; 139:613–6. [PubMed: 27016137]
28. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case-control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol. 2001; 30:1428–37. [PubMed: 11821358]
29. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, Ritz B. Perinatal characteristics and retinoblastoma. Cancer Causes Control. 2012; 23:1567–75. [PubMed: 22843021]
30. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975–2004. Br J Ophthalmol. 2009; 93:21–3. [PubMed: 18621794]
31. Van Maele-Fabry G, Lantin AC, Hoet P, Lison D. Childhood leukaemia and parental occupational exposure to pesticides: a systematic review and meta-analysis. Cancer Causes Control. 2010; 21:787–809. [PubMed: 20467891]
32. Ortega-Garcia JA, Lopez-Hernandez FA, Fuster-Soler JL, Martinez-Lage JF. Space-time clustering in childhood nervous system tumors in the Region of Murcia, Spain, 1998–2009. Child's Nervous System. 2011; 27:1903–11.
33. Greenop KR, Peters S, Bailey HD, et al. Exposure to pesticides and the risk of childhood brain tumors. Cancer Causes Control. 2013; 24:1269–78. [PubMed: 23558445]
34. Moore A, Enquobahrie DA. Paternal occupational exposure to pesticides and risk of neuroblastoma among children: a meta-analysis. Cancer Causes Control. 2011; 22:1529–36. [PubMed: 21879285]
35. Grube, A., Donaldson, D., Kiely, T., Wu, L. Pesticide industry sales and usage: 2006 and 2007 market estimates. Washington, DC: US Environmental Protection Agency; 2011.
36. Little MP, Kleinerman RA, Stiller CA, Li G, Kroll ME, Murphy MF. Analysis of retinoblastoma age incidence data using a fully stochastic cancer model. Int J Cancer. 2012; 130:631–40. [PubMed: 21387305]
37. Draper GJ, Sanders BM, Brownbill PA, Hawkins MM. Patterns of risk of hereditary retinoblastoma and applications to genetic counselling. Br J Cancer. 1992; 66:211–9. [PubMed: 1637670]
38. Dyer MA. Mouse models of childhood cancer of the nervous system. J Clin Pathol. 2004; 57:561–76. [PubMed: 15166259]
39. DiCiommo D, Gallie BL, Bremner R. Retinoblastoma: the disease, gene and protein provide critical leads to understand cancer. Semin Cancer Biol. 2000; 10:255–69. [PubMed: 10966849]
40. Morton, LM., Wong, JR., Gallie, BL., et al. Specific RB1 mutations and risk of subsequent neoplasms among survivors of hereditary retinoblastoma. American Association for Cancer Research Annual Meeting; Washington, D.C. 2013;
41. Bunin GR, Vardhanabhuti S, Lin A, Anschuetz GL, Mitra N. Practical and analytical aspects of using friend controls in case-control studies: experience from a case-control study of childhood cancer. Paediatr Perinat Epidemiol. 2011; 25:402–12. [PubMed: 21819422]
42. Rull RP, Ritz B, Shaw GM. Validation of self-reported proximity to agricultural crops in a case-control study of neural tube defects. J Expo Sci Environ Epidemiol. 2006; 16:147–55. [PubMed: 16047039]
43. Davis JR, Brownson RC, Garcia R. Family pesticide use in the home, garden, orchard, and yard. Arch Environ Contam Toxicol. 1992; 22:260–6. [PubMed: 1616309]

Table 1

Demographic characteristics of participants and crude conditional effect estimates[a]

	Unilateral (N=99 pairs)			Bilateral (N=56 pairs)		
	Case N (%)	**Control N (%)**	**Crude OR (95% C.I.)**	**Case N (%)**	**Control N (%)**	**Crude OR (95% C.I.)**
Child's sex						
Male	50 (51)	45 (45)	1.0	29 (52)	25 (45)	1.0
Female	49 (49)	48 (48)	0.9 (0.5–1.6)	27 (48)	30 (54)	0.8 (0.4–1.7)
Mother's Race						
White Non-Hispanic	68 (69)	74 (75)	1.0	44 (79)	37 (66)	1.0
Hispanic	19 (19)	11 (11)	9.4 (1.2–74.5)	5 (9)	7 (13)	N/A
Other	12 (12)	10 (10)	1.4 (0.4–4.9)	7 (13)	7 (13)	N/A
Mother's Age						
<30	52 (53)	44 (44)	1.0	22 (39)	21 (38)	1.0
30–34	32 (32)	37 (37)	0.7 (0.3–1.5)	18 (32)	21 (38)	0.9 (0.4–2.4)
35+	15 (15)	14 (14)	0.9 (0.3–2.5)	16 (29)	9 (16)	2.5 (0.6–10.7)
Maternal Education						
High School or Less	18 (18)	17 (17)	1.0 (0.3–3.0)	9 (16)	4 (7)	5.8 (0.7–51.3)
Vocational or Some	15 (15)	17 (17)	0.8 (0.3–2.0)	9 (16)	9 (16)	1.3 (0.4–4.3)
College						
College Graduate	48 (48)	40 (40)	1.0	24 (43)	23 (41)	1.0
Post-College	18 (18)	21 (21)	0.8 (0.3–2.0)	14 (25)	15 (27)	0.6 (0.2–2.1)
Number of prior pregnancies						
0	35 (35)	33 (33)	1.0	22 (39)	22 (39)	1.0
1	34 (34)	24 (24)	1.4 (0.7–3.1)	18 (32)	15 (27)	1.3 (0.5–3.4)
2	18 (18)	20 (20)	0.9 (0.4–2.0)	9 (16)	10 (18)	1.1 (0.3–3.6)
3+	11 (11)	16 (16)	0.6 (0.2–1.8)	7 (13)	4 (7)	1.9 (0.4–9.1)
Family Income						
<$25000	5 (5)	7 (7)	4.3 (0.6–30.6)	9 (16)	4 (7)	N/A
$25000–<$35000	7 (7)	6 (6)	3.6 (0.7–19.0)	1 (2)	4 (7)	N/A
$35000–<$50000	16 (16)	11 (11)	1.8 (0.5–5.9)	9 (16)	6 (11)	2.0 (0.2–25.6)
$50000–<$75000	24 (24)	19 (19)	1.7 (0.7–4.1)	11 (20)	15 (27)	0.3 (0.1–2.1)

	Unilateral (N=99 pairs)			Bilateral (N=56 pairs)		
	Case N (%)	**Control N (%)**	**Crude OR (95% C.I.)**	**Case N (%)**	**Control N (%)**	**Crude OR (95% C.I.)**
$75000–<$100000	12 (12)	15 (15)	1.2 (0.4–3.2)	6 (11)	8 (14)	0.3 (0.0–1.9)
≥$100000	24 (24)	29 (29)	1.0	15 (27)	11 (20)	1.0
Father's Race						
White Non-Hispanic	62 (62)	69 (70)	1.0	37 (66)	35 (63)	1.0
Hispanic	16 (16)	14 (14)	1.5 (0.3–6.9)	9 (16)	8 (14)	1.8 (0.2–15.4)
Other	13 (13)	8 (8)	2.3 (0.7–7.6)	9 (16)	8 (14)	1.3 (0.2–9.3)
Father's Age						
<30	29 (29)	34 (34)	1.0	12 (21)	17 (30)	1.0
30–34	33 (33)	29 (29)	1.3 (0.6–3.0)	21 (38)	18 (32)	1.8 (0.6–5.4)
35+	28 (28)	28 (28)	1.3 (0.5–3.6)	21 (38)	17 (30)	2.6 (0.7–9.4)

[a] All columns do not add to 100% due to missing information

Table 2

Estimate Effects and 95% CIs for parental pesticide exposure inside or outside the home in the month before or during pregnancy and unilateral retinoblastoma, conditional logistic regression analyses

	Cases (N=99)		Controls (N=99)		Crude	Adjusted[a]
	Exposed N	**Unexposed N**	**Exposed N**	**Unexposed N**	**OR**	**OR (95% CI)**
Professional services use						
Lawn or landscape services	21	78	13	86	2.5	2.8 (1.0, 8.2)
Home pest control services	12	87	20	79	0.4	0.6 (0.2, 1.7)
Product to kill insects or diseases						
Inside or outside the home, such as Raid	51	48	42	57	1.8	2.8 (1.1, 6.7)
On the lawn	13	86	9	90	1.5	1.2 (0.4, 3.4)
On plants, vegetables, fruit, flowers or trees	4	95	7	92	0.6	0.6(0.2, 2.3)
Use of weed control products on garden/lawn	27	72	19	80	1.8	2.3 (0.9, 5.4)
Use of product to kill mold or fungus	5	94	4	95	1.5	3.2 (0.4, 26.0)
Use of rodent control products	7	92	8	91	0.9	0.8 (0.3, 2.7)
Use of flea/tick products on pets	36	60	33	66	1.1	1.5 (0.7, 3.1)
Use of insect repellant	25	74	28	71	0.7	0.6 (0.3, 1.5)

[a] Adjusted for mother's race, mother's age, mother's work status, and whether the father was living at home at start of pregnancy.

Table 3

Estimate Effects and 95% CIs for parental pesticide exposure inside or outside the home in the month before or during pregnancy and bilateral retinoblastoma, conditional logistic regression analyses

	Cases (N=56)		Controls (N=56)		Crude	Adjusted[a]
	Exposed N	Unexposed N	Exposed N	Unexposed N	OR	OR (95% CI)
Professional Services Use						
Lawn or landscape services	14	42	7	49	3.0	3.4 (0.6, 18.0)
Home pest control services	13	43	11	45	1.8	1.0 (0.2, 5.7)
Product to kill insects or diseases						
Inside or outside the home, such as Raid	27	29	20	36	1.3	1.2 (0.4, 3.5)
On the lawn	5	51	1	55	4.0	12.5 (0.5, 322.1)
On plants, vegetables, fruit, flowers or trees	6	50	2	54	4.0	NA
Use of weed control products on garden/lawn	15	41	12	44	1.2	1.0 (0.3, 3.3)
Use of product to kill mold or fungus	1	55	1	55	NA	NA
Use of rodent control products	8	48	4	52	2.5	2.5 (0.2, 26.9)
Use of flea/tick products on pets	21	35	15	41	1.9	1.9 (0.6, 5.8)
Use of insect repellant	13	43	13	43	1.0	1.3 (0.3, 5.6)

[a]Adjusted for mother's race, mother's age, mother's work status, father's age and whether the father was living at home at start of pregnancy.

Table 4

Effect estimates and 95% CI for combined parental pesticide exposures in the month before or during pregnancy and sporadic retinoblastoma, conditional logistic regression

	Unilateral (N=99 pairs)				Bilateral (N=56 pairs)			
	Cases	Controls	Crude OR	Adjusted OR (95% CI)[a]	Cases (N=56)	Controls (N=56)	Crude OR	Adjusted OR (95% CI)[a]
Type of pesticide used								
None used	31	32	Ref	Ref	13	21	Ref	Ref
Spray	49	41	1.6	2.4 (0.9, 6.0)	26	19	2.1	2.8 (0.7, 12.3)
Other[b]	18	20	1.1	1.4 (0.6, 3.7)	17	12	2.8	4.1 (0.9, 20.1)
Where was the pesticide was used								
None used	35	38	Ref	Ref	19	27	Ref	Ref
Inside home	33	31	1.5	2.5 (0.9, 7.0)	23	11	2.3	1.9 (0.6, 6.1)
Outside home	30	24	1.7	2.5 (1.0, 6.5)	14	14	1.3	1.9 (0.5, 6.8)
When was the pesticide was used								
None used	20	22	Ref	Ref	10	15	Ref	Ref
In the month before pregnancy or first trimester	55	47	1.4	1.7 (0.6, 4.6)	31	25	2.0	1.9 (0.4, 8.4)
In second or third trimester	23	24	1.3	1.4 (0.4, 4.4)	15	12	1.7	3.1 (0.7, 14.0)
Who applied the pesticides								
None used	19	20	Ref	Ref	10	15	Ref	Ref
Mother	44	44	1.1	1.7 (0.6, 4.7)	24	19	2.0	2.5 (0.6, 10.7)
Father or other	35	29	1.4	2.4 (0.8, 7.1)	22	18	1.7	2.4 (0.5, 10.4)
Frequency of pesticide use								
None used	20	21	Ref	Ref	10	15	Ref	Ref
Most days or 1 to 3 times a week	15	19	1.0	1.5 (0.5, 5.2)	12	7	1.0	1.5 (0.5, 5.2)
1 to 3 times a month, less than 1 time a month or once or twice only	63	53	1.3	1.8 (0.7, 4.8)	34	30	1.3	1.8 (0.7, 4.8)

[a] Adjusted for mother's race, mother's age, mother's work status, and whether the father was living at home at start of pregnancy

[b] Other types of pesticides include liquids, granules, foggers, powders, baits or traps.