HHS Public Access

Author manuscript

Pediatr Blood Cancer. Author manuscript; available in PMC 2017 September 01.

Published in final edited form as:

Pediatr Blood Cancer. 2016 September ; 63(9): 1557–1562. doi:10.1002/pbc.26065.

The Role of Childhood Infections and Immunizations on Childhood Rhabdomyosarcoma: A Report from the Children's Oncology Group

Hari Sankaran[1], **Heather E. Danysh**[1], **Michael E. Scheurer**[1], **M. Fatih Okcu**[1], **Stephen X. Skapek**[2], **Douglas S. Hawkins**[3], **Logan G. Spector**[4], **Erik B. Erhardt**[6], **Seymour Grufferman**[7], and **Philip J. Lupo**[1]

[1] Department of Pediatrics, Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA

[2] Children's Medical Center, University of Texas Southwestern Medical Center, Dallas, TX, USA

[3] Seattle Children's Hospital, University of Washington, and Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[4] Division of Pediatric Epidemiology and Clinical Research, Department of Pediatrics, University of Minnesota, Minneapolis, MN, USA

[6] Department of Mathematics and Statistics, University of New Mexico, Albuquerque, NM, USA

[7] Division of Epidemiology and Biostatistics, Department of Internal Medicine, University of New Mexico, Albuquerque, NM, USA

Abstract

Background—Rhabdomyosarcoma (RMS) is a rare, highly malignant tumor arising from primitive mesenchymal cells that differentiate into skeletal muscle. Relatively little is known about RMS susceptibility. Based on growing evidence regarding the role of early immunologic challenges on RMS development, we evaluated the role of infections and immunizations on this clinically significant pediatric malignancy

Procedure—RMS cases (n=322) were enrolled from the third trial coordinated by the Intergroup Rhabdomyosarcoma Study Group. Population-based controls (n=322) were pair matched to cases on race, sex, and age. The following immunizations were assessed: diphtheria-pertussis-tetanus (DPT), measles-mumps-rubella (MMR), and oral polio vaccine (OPV). We also evaluated if immunizations were complete vs. incomplete. We examined selected infections including chickenpox, mumps, pneumonia, scarlet fever, rubella, rubeola, pertussis,

Corresponding Author: Philip J. Lupo, PhD, MPH, One Baylor Plaza, MS: BCM305, Houston, TX 77030 USA, Phone: 713-798-2960, Philip.Lupo@bcm.edu.

Novelty and impact: Relatively little is known regarding the epidemiology of rhabdomyosarcoma (RMS), a malignant tumor of developing muscle. Though the protective effect of immunizations and infections has been studied in other childhood cancers, this has not been well described in childhood RMS. Utilizing data from the largest case-control study of childhood RMS, we found that certain immunizations are associated with a protective effect in childhood RMS. Further research is needed to understand the biological mechanism for these associations.

Conflict of Interest

The authors have no conflict to declare.

mononucleosis, and lung infections. Conditional logistic regression models were used to calculate an odds ratio (OR) and 95% confidence interval (CI) for each exposure, adjusted for maternal education and total annual income

Results—Incomplete immunization schedules (OR=5.30, 95% CI: 2.47-11.33) and incomplete DPT immunization (OR=1.56, 95% CI: 1.06-2.29) were positively associated with childhood RMS. However, infections did not appear to be associated with childhood RMS.

Conclusions—This is the largest study of RMS to date demonstrating a possible protective effect of immunizations against development of childhood RMS. Further studies are needed to validate our findings. Our findings add to the growing body of literature suggesting a protective role of routine vaccinations in childhood cancer and specifically in childhood RMS.

Keywords

immunizations; infections; epidemiology; rhabdomyosarcoma; soft tissue sarcoma

Introduction

Rhabdomyosarcoma (RMS) is a highly malignant tumor of developing skeletal muscle that can occur anywhere in the body. Although RMS is the most common soft tissue sarcoma in children,[1,2] the annual incidence is only 4.6 per million in those younger than 20 years of age.[3] In the United States, about 350 children and adolescents are diagnosed with RMS per year, and half of those cases occur before 10 years of age.[3] Five-year survival for RMS is 65% for those diagnosed less than 15 years of age, making it one of the worst childhood cancers in terms of survival.[4]

Very few susceptibility factors have been identified for childhood RMS. Previous studies have suggested a potential role for prenatal X-ray exposure,[5] parental drug use,[6] advanced maternal age, and large for gestational age at birth[7] in the etiology of childhood RMS. However, few of these factors have been validated in independent assessments. Furthermore, confirmed risk factors for RMS such as familial genetic syndromes account for less than 5% of cases.[8-10] Because of this, there is a need to identify novel susceptibility factors, which may shed light on the etiology of these rare, but clinically significant malignancies.

A long-suspected risk factor for childhood malignancies is related to the disruption of immune system development.[11,12] Several studies have evaluated the role of early infections, immunizations, and atopic conditions on multiple childhood malignancies including childhood acute lymphoblastic leukemia (ALL), neuroblastoma, and brain tumors.[13-15] Additionally, there is recent evidence from our group suggesting atopic conditions are inversely associated with childhood RMS,[16] which is similar to the association observed with childhood ALL.[11] While childhood infections and immunizations have been evaluated in relation to ALL and other childhood malignancies, there have been limited assessments of these factors on childhood RMS. Therefore, the goal of this study was to determine the role of infections and immunizations on childhood RMS using data from the largest case-control study of RMS to date.

Methods

Study Population

RMS cases were enrolled in the third trial previously coordinated by the Intergroup Rhabdomyosarcoma Study Group (IRS-III), which became part of the Children's Oncology Group in 2000 and managed treatment protocols for 80-85% of all childhood RMS cases in the United States.[17] The details regarding the case-control study have been previously described.[5,6,18] Briefly, newly diagnosed RMS cases 0-20 years of age were enrolled in the IRS-III study between April 1982 and July 1988. Central expert pathology review confirmed all RMS diagnoses as well as the histologic subtype (i.e., embryonal, alveolar, or not otherwise specified [NOS]). Of the 511 childhood RMS patients enrolled in IRS-III during the study period, 440 cases were eligible for the current study, and 351 had completed interviews. Of the 71 ineligible cases, 29 had no home telephone, nine were not citizens of the United States, 15 were from families that did not speak English or Spanish, 18 were treated in institutions where the study was not approved by the institutional review board. An additional 89 cases did not participate due to parental (n=41) or physician (n=30) refusal, and 18 families could not be located. Seventy-three percent (n=322) of eligible and interviewed cases were matched with controls.[5,6,18]

Random-digit dialing was used to recruit controls during the same time period in which cases were enrolled.[5,6,18] Specifically, the telephone area code and first five digits of the cases' phone number were used with two randomly selected terminal digits to search for matching controls. Controls were pair-matched to cases on race, sex, and age (within one year for cases aged 0-5 years at diagnosis, and within three years for cases aged 5-20 years at diagnosis). Twenty-two percent of homes with a matching child refused to participate, and controls could not be identified for 8% of cases.[5,6,18]

Data Collection and Variables

Data were collected from case and control families by telephone interview at the time of enrollment using a structured questionnaire. The child's mother and father were asked to participate in the interview, which for case and control families lasted on average 70 and 68 minutes, respectively. Interviews were conducted in English and Spanish (six case families and two control families were Spanish-speaking). The interview included questions about childhood environmental exposures, parental occupational exposures, family demographic characteristics, parental lifestyle and behavioral characteristics, and medical history. On average, parents were asked to recall exposures that occurred eight to nine years prior to the interview.

For this analysis, we focused on the child's immunization history and childhood infections as potential risk factors for RMS. We evaluated the following questionnaire items related to immunizations: "Is your child up-to-date on his immunizations;" "Has your child had the following immunizations: 1) diphtheria, tetanus, pertussis (DPT), 2) measles, mumps, rubella (MMR), 3) Oral polio vaccine (OPV), 4) hepatitis B, 5) smallpox, and 6) Bacillus Calmette–Guérin (BCG)"; and "How many doses of these immunizations did your child receive." In addition, the parents were asked about the child's infection history: "Did your

child have any of the following infections before diagnosis: 1) chicken pox, 2) mumps, 3) German measles (rubella), 4) red measles (rubeola), 5) whooping cough, 6) scarlet fever, 7) rheumatic fever, 8) pneumonia, 9) tuberculosis, 10) other lung infections, 11) infectious mononucleosis, and 12) meningitis."

The American Academy of Pediatrics (AAP) immunization schedule during the study period (1980s) was used to create composite variables regarding completion of primary immunization series for each individual vaccine of interest and combination vaccines. According to the AAP completion of primary immunizations for an 18 month old child includes the receipt of the following set of vaccines: a) three doses of OPV, b) four doses of DPT, c) one dose of MMR vaccine.

Covariates for this analysis were selected *a priori* based on previous literature [12,19,20] and included: ethnicity of child (non-Hispanic or Hispanic); maternal education (less than high school, high school, or more than high school); paternal education (less than high school, high school, or more than high school); and total annual household income in United States Dollars (categorized as <$20,000, $20,000-$39,999, ≥$40,000 based on annual incomes during the study period). Additionally, the following matching factors were included in all statistical models: sex of child (male or female); race of child (white, black, or other); and age at diagnosis/enrollment (years).

Statistical Analyses

Descriptive statistics were used to characterize the demographic features among cases and controls. Frequency distributions were tabulated for categorical variables, and means and standard deviations were calculated for continuous variables. Conditional logistic regression was used to calculate an odds ratio (OR) and 95% confidence interval (CI) to determine the association between each demographic factor and childhood RMS. In order to evaluate the role of childhood infections and immunizations on childhood RMS, conditional logistic regression was used to generate adjusted ORs (aORs) and 95% CIs. Associations were considered statistically significant if $P<0.05$. A test for linear trend was used to examine the association between aORs and an ordinal variable with more than two categories. Associations were considered statistically significant if $P<0.05$. Maternal education and total annual income were included in final models *a priori*.[5,6,17,21] Because the RMS histologic subtypes are suspected to be heterogeneous in etiology, the association of selected variables and childhood RMS was also assessed separately for children diagnosed with embryonal RMS and those diagnosed with alveolar RMS. All analyses were conducted using Stata 13.1 (StataCorp LP, College Station, TX).

Results

Selected demographic factors among RMS cases and controls are presented in Table 1. Sex, age at diagnosis/enrollment, and race were similar between childhood RMS cases (n=322) and controls (n=322), as these were matching factors. Cases were more likely to live in homes where the total annual income was less than $20,000 compared to controls (OR=1.61, 95% CI: 1.11-2.34). Case mothers and fathers were more likely to have less education beyond high school compared to control mothers and fathers (OR=1.10, 95%CI: 0.67-1.80

and OR=1.45, 95% CI: 0.88-2.37, respectively). The majority of RMS cases were diagnosed with embryonal (*n*=215, 66.7%), followed by alveolar (*n*=66, 20.5%), and NOS (*n*=41, 12.8%).

Overall, there were no statistically significant associations detected between selected infections and childhood RMS (Table 2). Among the infections evaluated, inverse associations with childhood RMS were observed with exposure to chickenpox (OR=0.71, 95% CI: 0.49-1.04), mumps (OR=0.69, 95% CI: 0.31-1.52), rubella (OR=0.80, 95% CI: 0.45-1.42), and rubeola (OR=0.83, 95% CI: 0.32-2.10). Although lung infections had an inverse association in children with RMS (OR=0.64, 95% CI: 0.40-1.01), pneumonia was found to have a positive association (OR=1.17, 95% CI: 0.72-1.90). Due to an insufficient number of exposed cases and controls, some infections were either not estimated (i.e., tuberculosis and meningitis) or had imprecise confidence intervals (i.e., mononucleosis and pertussis). No differences were seen when results were stratified based on histology (data not shown), therefore results are presented for all RMS cases combined.

Immunizations and their associations with childhood RMS are presented in Table 3. Most parents (97.2% of case parents and 98.4% of control parents) provided information on their child's immunization history. DPT, MMR, and OPV were defined as complete based on the number of vaccinations received as defined by the AAP, and age was addressed by using a pair-matched data set. Children with RMS were more likely to have incomplete immunization schedules compared to controls (OR=5.30, 95% CI: 2.47-11.33). A statistically significant trend (P=0.022) was seen between an incomplete series (OR=1.56, 95% CI: 1.06-2.29) or no doses (OR=1.74, 95% CI: 0.73-4.15) of the DPT vaccine and childhood RMS. A similar trend (P=0.026) was seen for an incomplete series (OR=1.42, 95% CI: 0.86-2.35) or no doses (OR=1.87, 95% CI: 1.00-3.50) of OPV and RMS. While there was a positive and significant association between no doses of the MMR vaccine and childhood RMS in unadjusted analyses (OR=1.57, 95% CI: 1.02-2.40), this did not hold after adjusting for total annual income and maternal education (OR=1.43, 95% CI: 0.94-2.21).

Discussion

Overall, our results suggest that incomplete or lack of immunizations was positively associated with childhood RMS risk. Specifically, children with incomplete immunizations according to the AAP were 5-times more likely to develop RMS compared to those with complete immunizations. Specific incomplete immunizations that were associated with childhood RMS were the MMR vaccine and the OPV vaccine. While the incomplete DPT vaccine was not significantly associated with childhood RMS, the direction of effect was consistent.

There was little evidence that infections were associated with childhood RMS. However our findings of an inverse association with chickenpox infection and childhood RMS are consistent with a previous study on the role of chickenpox infection and glioma risk (OR=0.59, 95% CI: 0.40-0.86).[22] The expansion of varicella zoster-specific CD4 and CD8 T cells elicited in response to the varicella vaccine occurs in a similar fashion as that of

naturally-acquired chickenpox infection.[23] Therefore, future studies of this association with RMS should include the evaluation of varicella vaccine, which is part of the current AAP immunization schedule, in addition to chickenpox infection.

Our findings of the protective effect of immunizations on childhood RMS risk are consistent with a previous report of childhood RMS. In a smaller study of RMS using another population (*n*=33 cases), more cases were incompletely immunized compared to controls, similar to our study population.[21] While the findings were not statistically significant, childhood RMS was inversely associated with complete immunizations (OR=0.7, 95% CI: 0.1-7.6), DPT (OR=0.7, 95% CI: 0.1-7.6), and MMR (OR=0.3, 95% CI: 0.1-1.5). Furthermore, our results related to childhood infections are largely similar. Specifically, their findings were mixed and not statistically significant.[21]

Childhood immunizations have been associated with other childhood malignancies, most notably childhood ALL. In one case-control study of childhood ALL (*n*=63 cases), cases were less likely to be immunized against measles compared to controls (RR=0.2, 95% CI: 0.1-0.7).[24] A larger, more recent case-control study of childhood ALL (*n*=323 cases) also found that cases were less likely to be fully immunized against *Haemophilus influenzae* type b compared to controls (OR=0.55, 95% CI: 0.32-0.97).[25] Similar associations have also been reported for childhood lymphomas and acute myelogenous leukemia.[26]

The mechanisms underlying these associations are unclear. However, it is believed that early immunologic stimuli, including vaccines, stimulate the developing immune system, possibly promoting the anti-tumor activity of T-helper Type 2 (Th2), T-helper Type 1 (Th1), and natural killer (NK) cells.[27] Specifically, immunologic responses to vaccines are determined by the dosing interval and the child's age, which is reflected in the AAP immunization schedule. The effects of these early childhood vaccination responses are unique as they are predominantly Th2 responses, and completion of vaccination schedules can lead to the persistence of immune memory.[28] This immunologic priming has been theorized to modulate the adaptive immune system to recognize and eliminate malignant cells and control their growth.[29] The anti-tumor effect of Th2 cells is due in part to eosinophil-mediated tumor clearance and also through the release of cytokines including interleukin (IL)-4 and IL-10, which ultimately inhibit angiogenesis and inflammation.[30] Notably, live (e.g., MMR) and killed vaccines (e.g., DPT, OPV) elicit responses predominantly from Th1 or Th2 cells, respectively. Th1 anti-tumor activity is thought to play a role through interferon (IFN)-gamma, which stimulates macrophages and CD8+ cytotoxic T cell infiltration limiting tumorigenic activity.[30] Specific to RMS risk, Th2 response appears to play a role in the differentiation phase of myogenesis through recruitment of macrophages and secretion of IL-4 and IL-10. Disruption of this process halts maturation of regenerating skeletal muscle and increases myoblast proliferation through persistence of IL-6.[31]

Our study must be considered in light of certain limitations. As information on immunizations was obtained through a structured questionnaire, there is a potential for recall bias (i.e., mothers of cancer patients may be more likely to accurately report childhood infections and immunization status in light of their child's cancer diagnosis). Though it is

difficult to discern if recall bias influenced our findings, our results are consistent with several studies evaluating immunizations and leukemia,[13,32,33] as well as RMS and neuroblastoma.[14,21] Furthermore, a study evaluating parental report of childhood vaccinations indicated that recall of completeness of vaccines was similar to provider-based records.[21] Finally, vaccination coverage in our study population is similar to national estimates during the same period.[25] Another limitation of our study is the age of the dataset, which resulted in the inability to evaluate newer vaccines including hepatitis A and B, varicella, injectable polio, pneumococcal, *Haemophilus influenzae* type b, and rotavirus.[34]

Our study has several strengths, including being the largest case-control study of childhood RMS with all cases centrally reviewed by the IRS Group. Cases were enrolled from all across the United States and matched controls were selected via random-digit dialing methods to reduce bias due to geographic variability. The response rate was high among cases (92%) and controls (78%), which was comparable to other studies utilizing random digit dialing as a selection method for controls during that time period.[35]

In summary, our findings suggest that immunizations may decrease the risk of childhood RMS. Our results are consistent with associations seen with other childhood malignancies.[13,24,26,33] However, our findings must be validated in larger and contemporary populations. Specifically, future studies will need to take into consideration the ever growing landscape of vaccination schedules and whether specific vaccines or vaccinations overall play a role in childhood RMS. Ultimately, our findings add to the growing body of evidence suggesting the importance of immune regulation on childhood cancer incidence.

Acknowledgements

This work was supported by the U.S. National Institutes of Health Training Program in Pediatric Cancer Epidemiology and Control grant R25 CA160078 (M. Scheurer); U.S. National Cancer Institute (NCI) grants CA21244, CA24507, CA30318, CA30969, CA29139, and CA13539; and in part by the Kurt Groten Family Research Scholars Award (P. Lupo), CPRIT RP140258 (P. Lupo), and Alex's Lemonade Stand Foundation Epidemiology Grant (P. Lupo).

Abbreviations

RMS	rhabdomyosarcoma
OR	odds ratio
DPT	diphtheria-pertussis-tetanus
MMR	measles-mumps-rubella
OPV	oral polio vaccine
CI	confidence interval
IRS	Intergroup Rhabdomyosarcoma Study
AAP	American Academy of Pediatrics

ALL	acute lymphoblastic leukemia
Th-2	T-helper Type 2
Th-1	T-helper Type 1
IFN	interferon

References

1. Li J, Thompson TD, Miller JW, Pollack LA, Stewart SL. Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics. 2008; 121(6):e1470–1477. [PubMed: 18519450]
2. Ognjanovic S, Linabery AM, Charbonneau B, Ross JA. Trends in childhood rhabdomyosarcoma incidence and survival in the United States, 1975-2005. Cancer. 2009; 115(18):4218–4226. [PubMed: 19536876]
3. Gurney JG, Young JL Jr. Roffers SD, Smith MA, Bunin GR. Soft Tissue Sarcomas. Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995: National Cancer Institute SEER Program. 1999
4. Pizzo, P.; Poplack, D. Epidemiology of Childhood Cancer.. In: Philip, A.; Pizzo, DP., editors. Principles And Practice of Pediatric Oncology. Sixth Edition. Lippincott Williams & Wilkins; Two Commerce Square, 2001 Market Street, Philadelphia, PA 19103: 2011. p. 2-17.
5. Grufferman S, Ruymann F, Ognjanovic S, Erhardt EB, Maurer HM. Prenatal X-ray exposure and rhabdomyosarcoma in children: a report from the children's oncology group. Cancer Epidemiol Biomarkers Prev. 2009; 18(4):1271–1276. [PubMed: 19293315]
6. Grufferman S, Schwartz AG, Ruymann FB, Maurer HM. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes Control. 1993; 4(3):217–224. [PubMed: 8318638]
7. Lupo PJ, Danysh HE, Skapek SX, Hawkins DS, Spector LG, Zhou R, Okcu MF, Papworth K, Erhardt EB, Grufferman S. Maternal and birth characteristics and childhood rhabdomyosarcoma: a report from the Children's Oncology Group. Cancer Causes Control. 2014; 25(7):905–913. [PubMed: 24831857]
8. DeBaun MR, Tucker MA. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. J Pediatr. 1998; 132(3 Pt 1):398–400. [PubMed: 9544889]
9. Matsui I, Tanimura M, Noboru K, Tadashi S, Nagahara N, Akatsuka J. Neurofibromatosis type 1 and childhood cancer. Cancer. 1993; 72(9):2746–2754. [PubMed: 8402499]
10. Quezada E, Gripp K. Costello syndrome and related disorders. Current Opinion in Pediatrics. 2007; 19(6):636–644. [PubMed: 18025929]
11. Linabery AM, Jurek AM, Duval S, Ross JA. The association between atopy and childhood/adolescent leukemia: a meta-analysis. Am J Epidemiol. 2010; 171(7):749–764. [PubMed: 20228139]
12. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. Int J Cancer. 2006; 118(12):3124–3132. [PubMed: 16395696]
13. Pagaoa MA, Okcu MF, Bondy ML, Scheurer ME. Associations between vaccination and childhood cancers in Texas regions. J Pediatr. 2011; 158(6):996–1002. [PubMed: 21227448]
14. Menegaux F, Olshan AF, Neglia JP, Pollock BH, Bondy ML. Day care, childhood infections, and risk of neuroblastoma. American Journal of Epidemiology. 2004; 9(159):843–851. [PubMed: 15105177]
15. Rudant J, Orsi L, Menegaux F, Petit A, Baruchel A, Bertrand Y, Lambilliotte A, Robert A, Michel G, Margueritte G, Tandonnet J, Mechinaud F, Bordigoni P, Hemon D, Clavel J. Childhood acute leukemia, early common infections, and allergy: The ESCALE Study. Am J Epidemiol. 2010; 172(9):1015–1027. [PubMed: 20807738]

16. Lupo PJ, Zhou R, Skapek SX, Hawkins DS, Spector LG, Scheurer ME, Okcu MF, Melin B, Papworth K, Erhardt EB, Grufferman S. Allergies, atopy, immune-related factors and childhood rhabdomyosarcoma: A report from the children's oncology group. Int J Cancer. 2013
17. Grufferman S, Delzell E, Delong ER. An approach to conducting epidemiologic research within cooperative clinical trials groups. J Clin Oncol. 1984; 2(6):670–675. [PubMed: 6726305]
18. Yang P, Grufferman S, Khoury MJ, Schwartz AG, Kowalski J, Ruymann FB, Maurer HM. Association of childhood rhabdomyosarcoma with neurofibromatosis type I and birth defects. Genet Epidemiol. 1995; 12(5):467–474. [PubMed: 8557179]
19. Freiden T, Jaffe HW, Cono J, Richards CL. CDC Health Disparities and Inequalities Report — United States, 2013. Morbidity and Mortality Weekly Report. 2013; 62(3):1–27. [PubMed: 23302815]
20. Sebelius, K.; Frieden, TR.; Sondik, EJ. Health, United States, 2011: With Special Feature on Socioeconomic Status and Health. National Center for Health Statistics; Hyattsville, MD: 2011.
21. Grufferman S, Wang HH, DeLong ER, Kimm SY, Delzell ES, Falletta JM. Environmental factors in the etiology of rhabdomyosarcoma in childhood. J Natl Cancer Inst. 1982; 68(1):107–113. [PubMed: 6948120]
22. Wrensch M, Weinberg A, Wiencke J, Miike R, Sison J, Wiemels J, Barger G, DeLorenze G, Aldape K, Kelsey K. History of chickenpox and shingles and prevalence of antibodies to varicella-zoster virus and three other herpesviruses among adults with glioma and controls. Am J Epidemiol. 2005; 161(10):929–938. [PubMed: 15870157]
23. Arvin AM. Humoral and Cellular Immunity to Varicella-Zoster Virus: An Overview. The Journal of Infectious Diseases. 2008; 197(2):58–60. [PubMed: 18171285]
24. Nishi M, Miyake H. A case-control study of non-T cell acute lymphoblastic leukaemia of children in Hokkaido, Japan. J Epiemiol Community Health. 1989; 43(4):352–355.
25. Ma X, Does M, Metayer C, Russo C, Wong A, Buffler P. Vaccination history and risk of childhood leukaemia. Int J Epidemiology. 2005; 34(5):1100–1109.
26. McKinney PA, Cartwright RA, Saiu JM, Mann JR, Stiller CA, Draper GJ, Hartley AL, Hopton PA, Birch JM, Waterhouse JA, et al. The inter-regional epidemiological study of childhood cancer (IRESCC): a case control study of aetiological factors in leukaemia and lymphoma. Arch Dis Child. 1987; 62(3):279–287. [PubMed: 3646026]
27. Ellyard JI, Simson L, Parish CR. Th2-mediated anti-tumour immunity: friend or foe? Tissue Antigens. 2007; 70(1):1–11. [PubMed: 17559575]
28. Siegrist, C-A. Vaccines. Plotkin, SA.; Orenstein, WA.; Offit, PA., editors. Elsevier; 2013. p. 17-36.
29. Cramer DW, Finn OJ. Epidemiologic perspective on immune-surveillance in cancer. Current Opinion Immunology. 2011; 23(2):265–271.
30. Chow M, Moller A, Smyth MJ. Inflammation and immune surveillance in cancer. Seminars in Cancer Biology. 2012; 22:23–32. [PubMed: 22210181]
31. Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. Am J Physiol Regul Integr Comp Physiol. 2010; 298(5):R1173–1187. [PubMed: 20219869]
32. Auvinen A, Hakulinen T, Groves F. Haemophilus influenzae type B vaccination and risk of childhood leukaemia in a vaccine trial in Finland. British Journal of Cancer. 2000; 83(7):956–958. [PubMed: 10970701]
33. MacArthur AC, McBride ML, Spinelli JJ, Tamaro S, Gallagher RP, Theriault GP. Risk of childhood leukemia associated with vaccination, infection, and medication use in childhood: the Cross-Canada Childhood Leukemia Study. Am J Epidemiol. 2008; 167(5):598–606. [PubMed: 18079130]
34. AAP Recommended Immunization Schedules. American Academy of Pediatrics; 2015. <http://www2.aap.org/immunization/izschedule.html#Birthon>
35. Bunin GR, Spector LG, Olshan AF, Robison LL, Roesler M, Grufferman S, Shu XO, Ross JA. Secular trends in response rates for controls selected by random digit dialing in childhood cancer studies: a report from the Children's Oncology Group. Am J Epidemiol. 2007; 166(1):109–116. [PubMed: 17456476]

TABLE I

Demographic Characteristics of Childhood Rhabdomyosarcoma Cases and Controls

Characteristic	Controls N=322	Cases N=322	OR	95% CI
Sex of the child, *n* (%)				
Male	215 (66.8)	215 (66.8)	1.00	Ref.
Female	1.007 (33.2)	107 (33.2)	1.00	0.72-1.39
Race of child, *n* (%)				
White	291 (90.4)	287 (89.1)	1.00	Ref.
Black	21 (6.5)	20 (6.2)	0.97	0.51-1.82
Other	10 (3.1)	15 (4.7)	1.52	0.67-3.44
Ethnicity of child, *n* (%)				
Non-Hispanic	307 (95.9)	303 (94.7)	1.00	Ref
Hispanic	13 (4.1)	17 (5.3)	1.32	0.63-2.78
Age in years[a], mean (SD)	7.5 (5.4)	7.6 (5.3)	NE[b]	NE[b]
Maternal education, *n* (%)				
<High School	39 (11.8)	45 (14.1)	1.10	0.67-1.80
High School	126 (39.4)	132 (41.4)	1.00	Ref.
>High School	155 (48.4)	142 (44.5)	0.87	0.63-1.22
Paternal education, *n* (%)				
<High School	37 (11.8)	54 (17.1)	1.45	0.88-2.37
High School	111 (35.5)	112 (35.3)	1.00	Ref.
>High School	165 (52.7)	151 (47.6)	0.91	0.64-1.28
Total Annual income, *n* (%)				
<$20,000	77 (24.3)	104 (32.8)	1.61	1.11-2.35
$20,000-$39,999	155 (48.9)	131 (41.3)	1.00	Ref.
≥$40,000	85 (26.8)	82 (25.9)	0.68	0.78-1.67
Histologic subtypes, *n* (%)				
Embryonal		215 (66.7)		N/A
Alveolar		66 (20.5)		N/A
NOS		44 (12.8)		N/A

Abbreviations: OR=odds ratio; CI=confidence interval; SD=standard deviation

[c] NOS – not otherwise specified

[a] Age at diagnosis/enrollment

[b] NE – not estimated

TABLE II

Association Between Selected Infections with Childhood Rhabdomyosarcoma

Infection	Total N (%)	Controls N (%)	Cases N (%)	OR	95% CI	OR[a]	95% CI
Chickenpox							
No	326 (51.3)	152 (48)	174 (54.7)	1.00	Ref.	1.00	Ref.
Yes	309 (48.7)	165 (52)	144 (45.3)	0.71	0.49-1.04	0.71	0.48-1.04
Mumps							
No	604 (94.8)	299 (94.6)	305 (95)	1.00	Ref.	1.00	Ref.
Yes	33 (5.2)	17 (5.4)	16 (5)	0.75	0.35-1.59	0.69	0.31-1.52
Pneumonia							
No	565 (88)	284 (88.8)	281 (87.3)	1.00	Ref.	1.00	Ref.
Yes	77 (12)	36 (11.3)	41 (12.7)	1.17	0.72-1.90	1.25	0.75-2.09
Scarlet Fever							
No	624 (97.7)	310 (97.8)	314 (97.5)	1.00	Ref.	1.00	Ref.
Yes	15 (2.4)	7 (2.2)	8 (2.5)	1.00	0.35-2.85	0.99	0.34-2.85
Rubella							
No	576 (91.6)	284 (91)	292 (92.1)	1.00	Ref.	1.00	Ref.
Yes	53 (8.4)	28 (9)	25 (7.9)	0.85	0.49-1.49	0.80	0.45-1.42
Rubeola							
No	613 (96.7)	304 (96.2)	309 (97.2)	1.00	Ref.	1.00	Ref.
Yes	21 (3.3)	12 (3.8)	9 (2.8)	0.75	0.32-1.78	0.83	0.32-2.10
Pertussis							
No	634 (99.5)	318 (99.7)	316 (99.4)	1.00	Ref.	1.00	Ref.
Yes	3 (0.5)	1 (0.3)	2 (0.6)	2.00	0.18-22.01	2.45	0.21-28.21
Mononucleosis							
No	637 (99.1)	319 (99.4)	318 (98.8)	1.00	Ref.	1.00	Ref.
Yes	6 (0.9)	2 (0.6)	4 (1.2)	2.00	0.37-10.9	2.29	0.41-12.82
Lung infections							
No	546 (85.2)	263 (82.4)	283 (87.9)	1.00	Ref.	1.00	Ref.
Yes	95 (14.8)	56 (17.6)	39 (12.1)	0.64	0.40-1.01	0.65	0.40-1.04

Abbreviations: OR=odds ratio; CI=confidence interval. Cases and controls pair matched on race, sex, and age

[a]Adjusted for maternal education and total annual income (cases and controls pair matched on race, sex, and age)

TABLE III

Association of Immunization Schedules with Childhood Rhabdomyosarcoma

Immunization factors	Total N (%)	Controls N (%)	Cases N (%)	OR	95% CI	OR[a]	95% CI	P for trend[a]
Incomplete immunizations								
No	561 (90.5)	304 (96.2)	257 (84.5)	1.00	Ref.	1.00	Ref.	
Yes	59 (9.5)	12 (3.8)	47 (15.5)	4.50	2.27-8.93	5.30	2.47-11.33	
MMR vaccine								
Complete	502 (78.0)	261 (81.0)	241 (74.8)	1.00	Ref.	1.00	Ref.	
None	142 (22.1)	61 (18.9)	81 (25.2)	1.57	1.02-2.40	1.43	0.92-2.21	
DPT vaccine								
Complete	459 (71.2)	246 (76.4)	213 (66.2)	1.00	Ref.	1.00	Ref.	
Incomplete	162 (25.2)	67 (20.8)	95 (29.5)	1.66	1.15-2.40	1.56	1.06-2.29	
None	23 (3.6)	9 (2.8)	14 (4.3)	1.91	0.81-4.50	1.74	0.73-4.15	0.022
Oral polio vaccine								
Complete	459 (71.3)	246 (76.4)	213 (66.2)	1.00	Ref.	1.00	Ref.	
Incomplete	162 (25.2)	67 (20.8)	95 (29.5)	1.52	0.93-2.48	1.42	0.86-2.35	
None	23 (3.6)	9 (2.8)	14 (4.4)	1.69	0.95-3.03	1.87	1.00-3.50	0.026

Abbreviations: OR=odds ratio; CI=confidence interval. Cases and controls pair matched on race, sex, and age

[a]Adjusted for maternal education and total annual income (cases and controls pair matched on race, sex, and age)