

Allergies, atopy, immune-related factors and childhood rhabdomyosarcoma: a report from the Children's Oncology Group

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Rhabdomyosarcoma (RMS) is a highly malignant tumor of developing muscle that can occur anywhere in the body. Due to its rarity, relatively little is known about the epidemiology of RMS. Atopic disease is hypothesized to be protective against several malignancies; however, to our knowledge, there have been no assessments of atopy and childhood RMS. Therefore, we explored this association in a case-control study of 322 childhood RMS cases and 322 pair-matched controls. Cases were enrolled in a trial run by the Intergroup Rhabdomyosarcoma Study Group. Controls were matched to cases on race, sex and age. The following atopic conditions were assessed: allergies, asthma, eczema and hives; in addition, we examined other immune-related factors: birth order, day-care attendance and breastfeeding. Conditional logistic-regression models were used to calculate an odds ratio (OR) and 95% confidence interval (CI) for each exposure, adjusted for age, race, sex, household income and parental education. As the two most common histologic types of RMS are embryonal ($n = 215$) and alveolar ($n = 66$), we evaluated effect heterogeneity of these exposures. Allergies (OR = 0.60, 95% CI: 0.41–0.87), hives (OR = 0.61, 95% CI: 0.38–0.97), day-care attendance (OR = 0.48, 95% CI: 0.32–0.71) and breastfeeding for ≥ 12 months (OR = 0.36, 95% CI: 0.18–0.70) were inversely associated with childhood RMS. These exposures did not display significant effect heterogeneity between histologic types ($p > 0.52$ for all exposures). This is the first study indicating that atopic exposures may be protective against childhood RMS, suggesting additional studies are needed to evaluate the immune system's role in the development of this tumor.

Rhabdomyosarcoma (RMS) is a rare, 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 the annual incidence is only 4.6 per million in those younger than 20 years of age.² In the United States, about 350 children and adolescents are diagnosed with RMS per year,³ and half of those cases occur before 10 years of age.² The two major histologic subtypes of RMS are

embryonal (~70% of cases) and alveolar (~30% of cases), which is a distinct biological entity driven by a specific chromosomal translocation between either *PAX3* or *PAX7* and *FOXO1* in ~80% of cases.^{4–6}

Because of the rarity of these tumors, and the potential etiologic heterogeneity between subtypes, relatively little is known about the epidemiology and etiology of childhood RMS. Previous reports have tentatively identified a few potential risk factors, including prenatal X-ray exposure,⁷ maternal drug use,⁸ advanced maternal age,⁹ large for gestational age at birth⁹ and congenital malformations.¹⁰ Additionally, a small percentage of cases are associated with known genetic disorders, such as neurofibromatosis Type 1 and the Li-Fraumeni familial cancer syndrome.^{11,12} Because these risk factors do not account for a majority of cases, there is a need to identify additional risk factors for childhood RMS.

Allergies and atopic conditions (e.g., asthma, eczema and hives) have been evaluated as risk factors for several malignancies including childhood leukemia.^{13,14} In a recent meta-analysis, Linabery *et al.*¹³ reported an inverse association

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What's new?

According to immune surveillance theory, allergies and atopic disease may protect against certain childhood malignancies, most notably leukemia. The same associations, however, have not been explored for rhabdomyosarcoma (RMS), a rare and highly malignant disease, but the most common soft-tissue sarcoma in children. In this assessment, allergies, hives, day-care attendance, and breastfeeding (for 12 months or longer) were found to be inversely associated with childhood RMS. In addition, as the number of atopic conditions increased, RMS risk decreased. The results point to a possible role for the immune system in the development of childhood RMS.

between atopy/allergies and childhood acute lymphoblastic leukemia (ALL) [odds ratio (OR) = 0.69, 95% confidence interval (CI) = 0.54–0.89]. Additionally, other factors related to immune system development (birth order, day-care attendance and breastfeeding) seem to be associated with childhood malignancies, including ALL.^{15–17} It has been suggested that those with history of allergy and atopic conditions may have a greater capacity to detect and destroy aberrant cells, the so-called immune surveillance theory.¹⁴

Despite these associations, little work has been done to characterize the role of immune system development, allergies and atopy on childhood RMS risk. As childhood RMS seems to share some other risk factors with ALL including prenatal X-ray exposure,^{7,18} being born large for gestational age,^{9,19} having neurofibromatosis Type 1^{10,20} and having a congenital malformation,²¹ the goal of our study was to explore the association between atopic conditions, as well as other immune-related factors^{15,22–25} and childhood RMS. We used data from one of the largest case-control studies of childhood RMS with extensive questionnaire data to explore this association.

Material and Methods**Study population**

Details of this case-control study have been described previously.^{7,8,10} Briefly, cases were patients with RMS in one clinical trial conducted by the previous Intergroup Rhabdomyosarcoma Study Group (IRSG), which became part of the Children's Oncology Group (COG) in 2000. IRSG treatment protocols enrolled 80% to 85% of all childhood RMS cases in the United States.²⁶ For our study, cases were 0 to 20 years of age at diagnosis and were consecutively entered into IRS-III from April 1982 to July 1988. The diagnoses and histologic subtype (*i.e.*, embryonal, alveolar and other) of all cases were confirmed by central expert pathology review. There were 511 patients 0 to 20 years of age in IRS-III during the study period, of whom 440 cases were eligible for our study and 351 had completed interviews. Of the 71 ineligible cases: 29 had no home telephone; nine were not United States residents; 18 were treated in institutions that did not have Institutional Review Board approval and 15 came from families that did not speak English or Spanish. In addition, 89 eligible cases did not participate due to parental ($n = 41$) or physicians' ($n = 30$) refusals, whereas 18 families could not be located. In summary, 73% ($n = 322$) of eligible cases were interviewed and matched with controls.^{7,8,10}

Controls were selected by random-digit telephone dialing during the same period. Specifically, a case's area code and first five digits of the telephone number were used with two randomly selected terminal digits to search for a matching control. Controls were pair matched to cases on race, sex and age (within 1 year for cases aged less than 5 years and within 3 years for cases aged 5 to 20 years). Of homes with a matching child, 22% refused to participate.^{7,8,10}

Data collection and variables

Data were collected from case and control families by telephone interview using a structured questionnaire. Both mother and father were asked to participate in the interview. The mean duration of the interview was 70 min for case and 68 min for control families. Interviews were conducted in English or Spanish (six cases and two control families). The interview included questions about childhood and parental environmental exposures, conditions, lifestyles and behavioral factors. On average, parents were asked to recall exposures, which occurred 8 to 9 years before the interview.

For this analysis, we focused on the child's history of allergies and atopic conditions. Therefore, we evaluated the following questions: "Does your child have allergies?"; "Has your child ever had asthma?"; "Did your child have eczema before the date of diagnosis or enrollment in study?"; "Did your child have hives before the date of diagnosis or enrollment in study?" In addition, we examined the following immune-related factors: birth order (1, 2, ≥ 3); day-care attendance before kindergarten (no or yes); breastfeeding (no or yes) and breastfeeding duration in months (categorized as 0, < 6, 6–12, ≥ 12).

Covariates for this analysis were selected *a priori* based on previous literature¹⁴ 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, \geq \$40,000). Additionally, the following factors were included in all statistical models as they were matching factors: sex of child (male or female); race of child (white, black or other) and age at diagnosis/enrollment (years).

Statistical analysis

For categorical variables, frequency distributions were tabulated for cases and controls, while means and standard

Table 1. Characteristics of childhood rhabdomyosarcoma cases and controls

Characteristic	Cases, <i>n</i> (%), <i>n</i> = 322	Controls, <i>n</i> (%), <i>n</i> = 322
Sex of child		
Male	215 (66.8)	215 (66.8)
Female	107 (33.2)	107 (33.2)
Race of child		
White	287 (89.1)	291 (90.4)
Black	20 (6.2)	21 (6.5)
Other	15 (4.7)	10 (3.1)
Ethnicity of child		
Non-Hispanic	303 (94.7)	307 (95.9)
Hispanic	17 (5.3)	13 (4.1)
Age at diagnosis/ enrollment, mean years (SD)	7.6 (5.3)	7.5 (5.4)
Maternal education		
< High school	45 (14.1)	39 (12.2)
High school	132 (41.4)	126 (39.4)
> High school	142 (44.5)	155 (48.4)
Paternal education		
< High school	54 (17.1)	37 (11.8)
High school	112 (35.3)	111 (35.5)
> High school	151 (47.6)	165 (52.7)
Total annual household income		
< \$20,000	104 (32.8)	77 (24.3)
\$20,000–39,999	131 (41.3)	155 (48.9)
> \$40,000	82 (25.9)	85 (26.8)
Histologic subtypes		
Embryonal	215 (66.7)	
Alveolar	66 (20.5)	
NOS ¹	41 (12.8)	

¹Not other specified.

deviations were calculated by case status for continuous variables. Conditional logistic regression was used to calculate an adjusted OR (aOR) and 95% CI to evaluate the association between selected atopic conditions (and immune-related factors) and childhood RMS. For multinomial variables, the Cochran-Armitage test was used to calculate a *p* for trend. Additionally, we created a composite atopy variable based on the number of atopic conditions and other immune-related factors to explore a potential surrogate of atopy severity. Polytomous logistic regression, as proposed by Glynn and Rosner,²⁷ was used to evaluate effect heterogeneity among atopic conditions and childhood RMS histologic subtypes (*i.e.*, embryonal and alveolar). All analyses were performed using Stata 12.1 (StataCorp LP, College Station, TX).

Table 2. Selected atopic conditions and childhood rhabdomyosarcoma

Atopic condition	Controls, <i>n</i> (%)	Cases, <i>n</i> (%)	OR ¹	95% CI
Allergies				
No	196 (63.6)	237 (74.5)	1.00	Ref.
Yes	112 (36.4)	81 (25.5)	0.60	0.41–0.87
Asthma				
No	281 (89.5)	296 (92.8)	1.00	Ref.
Yes	33 (10.5)	23 (7.2)	0.66	0.37–1.18
Eczema				
No	301 (94.1)	305 (95.0)	1.00	Ref.
Yes	19 (5.9)	16 (5.0)	0.87	0.44–1.69
Hives				
No	260 (81.5)	279 (87.2)	1.00	Ref.
Yes	59 (18.5)	41 (12.8)	0.61	0.38–0.97

¹Adjusted for age, race and sex.

Results

The distribution of selected characteristics of RMS cases and controls are presented in Table 1. The most common histologic subtype of RMS in this population was embryonal (*n* = 215, 66.7%), followed by alveolar (*n* = 66, 20.5%) and not otherwise specified (NOS; *n* = 41, 12.8%). Cases and controls were similar on sex, race and age at diagnosis/enrollment due to matching. A higher proportion of case mothers (14.1%) and fathers (17.1%) had less than a high school education compared to control mothers (12.2%) and fathers (11.8%). Additionally, a higher proportion of cases (32.8%) were from households where the total annual income was less than \$20,000 compared to controls (24.3%).

The associations between selected atopic conditions and childhood RMS are presented in Table 2. There were inverse associations between allergies and childhood RMS (OR = 0.60, 95% CI: 0.41–0.87), as well as hives and childhood RMS (OR = 0.61, 95% CI: 0.38–0.97). Although children with RMS were less likely to have asthma (OR = 0.66, 95% CI: 0.37–1.18) or eczema (OR = 0.87, 95% CI: 0.44–1.69) compared to controls, these associations were not statistically significant. In this population, the prevalence of asthma (8.8%) and eczema (5.5%) was lower than allergies (30.8%) or hives (15.6%).

Increasing birth order was inversely associated with childhood RMS; however, it was not statistically significant (Table 3). Children with RMS were less likely to attend day care before kindergarten compared to controls (OR = 0.48, 95% CI: 0.32–0.71). Breastfeeding for 12 or more months was inversely associated with childhood RMS (OR = 0.36, 95% CI: 0.18–0.70) compared to no breastfeeding. Additionally, there was a statistically significant trend between increasing breastfeeding duration and childhood RMS (*p* = 0.01). Finally, children with RMS were less likely to have three or more atopic conditions (or other immune-related factors) compared to controls (OR = 0.22, 95% CI: 0.11–0.43), and

Table 3. Factors associated with immune system development, number of atopic conditions and childhood rhabdomyosarcoma

	Controls, n (%)	Cases, n (%)	OR ¹	95% CI
Birth order				
1	138 (43.3)	138 (43.4)	1.00	Ref.
2	101 (31.6)	102 (32.1)	0.95	0.64–1.39
≥ 3	80 (25.1)	78 (24.5)	0.86	0.55–1.33
				<i>p</i> for trend = 0.50
Day-care attendance				
No	145 (45.0)	191 (59.3)	1.00	Ref.
Yes	177 (55.0)	131 (40.7)	0.48	0.32–0.71
Breastfeeding				
No	142 (44.8)	156 (48.9)	1.00	Ref.
Yes	175 (55.2)	163 (51.1)	0.79	0.54–1.14
Breastfeeding duration, months				
0	143 (45.1)	163 (50.9)	1.00	Ref.
< 6	78 (24.6)	82 (25.6)	0.82	0.54–1.25
6–12	52 (16.4)	54 (16.9)	0.78	0.47–1.31
≥ 12	44 (13.9)	21 (6.6)	0.36	0.18–0.70
				<i>p</i> for trend = 0.01
Number of atopic conditions				
0	32 (9.9)	52 (16.1)	1.00	Ref.
1	70 (21.8)	104 (32.3)	0.70	0.39–1.26
2	67 (20.8)	83 (25.8)	0.51	0.27–0.96
≥ 3	153 (47.5)	83 (25.8)	0.22	0.11–0.43
				<i>p</i> for trend < 0.001

¹Adjusted for age, race, sex, household income, maternal and paternal education.

there was a statistically significant trend with increasing exposure to atopic conditions ($p < 0.001$).

Results for our analysis exploring effect heterogeneity among these atopic conditions and RMS histologic subtypes (*i.e.*, differing exposure effects by subtypes) are presented in Table 4. None of the atopic conditions or risk factors for atopic conditions displayed significant heterogeneity between embryonal and alveolar RMS (those subtypes that were NOS were not included due to potential within-group heterogeneity). Specifically, the p for heterogeneity was >0.52 for all exposures.

Discussion

In our study, several atopic conditions and factors associated with immune system development were inversely associated with childhood RMS including: allergies, hives, day-care attendance and breastfeeding for 12 or more months. Additionally, increasing number of atopic conditions (a potential surrogate of atopy severity) was associated with a decreasing

Table 4. Evaluation of effect heterogeneity among selected atopic conditions and childhood rhabdomyosarcoma histologic subtypes

Exposure	Embryonal rhabdomyosarcoma, n = 215		Alveolar rhabdomyosarcoma, n = 66		<i>p</i> for heterogeneity
	OR ¹	95% CI	OR ¹	95% CI	
Allergies					
No	1.00	Ref.	1.00	Ref.	
Yes	0.60	0.40–0.89	0.75	0.42–1.35	0.53
Hives					
No	1.00	Ref.	1.00	Ref.	
Yes	0.66	0.40–1.09	0.79	0.39–1.62	0.63
Day-care attendance					
No	1.00	Ref.	1.00	Ref.	
Yes	0.64	0.45–0.90	0.51	0.29–0.88	0.59
Breastfeeding duration, months					
0	1.00	Ref.	1.00	Ref.	
< 6	0.90	0.58–1.40	0.88	0.45–1.71	
6–12	0.88	0.53–1.47	0.63	0.26–1.54	
≥ 12	0.38	0.19–0.74	0.43	0.14–1.31	0.65
Number of atopic conditions					
0	1.00	Ref.	1.00	Ref.	
1	1.02	0.54–1.90	0.92	0.39–2.20	
2	0.70	0.36–1.35	0.80	0.32–1.98	
≥ 3	0.32	0.17–0.60	0.37	0.15–0.95	0.90

¹Adjusted for age, race and sex.

risk of childhood RMS. Although other atopic conditions (*e.g.*, asthma and eczema) were not significantly associated with childhood RMS, the direction of the association was consistent (*i.e.*, there was an inverse association between these conditions and childhood RMS). Additionally, these conditions were not as prevalent as the other factors evaluated in our study population.

To our knowledge, this is the first assessment of atopic conditions and childhood RMS. One previous study did indicate that childhood RMS cases had fewer immunizations than controls,²⁸ which is in keeping with a potential role of immunity on disease risk. Although little work has been done evaluating atopic conditions and childhood RMS, this question has been explored for other childhood malignancies. Specifically, in a meta-analysis of atopy and childhood ALL, Linabery *et al.*¹³ reported the following: atopy or allergies (summary OR = 0.69, 95% CI: 0.54–0.89); asthma (summary OR = 0.79, 95% CI: 0.61–1.02); hay fever (summary OR = 0.55, 95% CI: 0.46–0.55) and eczema (summary OR = 0.74, 95% CI: 0.58–0.96). These inverse associations are in keeping with our results. Additionally, investigators have reported inverse associations between childhood ALL and day-care attendance,¹⁵ breastfeeding^{16,24} and birth order.¹⁷ Interestingly, childhood ALL and RMS seem to have other

risk factors in common including being born large for gestational age,^{9,19} neurofibromatosis Type 1,^{10,20} having a congenital malformation^{10,21} and prenatal X-ray exposure.^{7,18}

The immune surveillance theory (*i.e.*, prophylaxis theory) is commonly used to explain the inverse associations that have been reported for atopic conditions and other childhood cancers, including ALL.^{13,14,29} According to this line of evidence, an atopic immune response may offer an advantage by destroying tumor cells as they arise, or by eliminating carcinogenic exposures.^{14,22,30} Although the biology behind the immune surveillance theory is not firmly established, there is evidence that T helper Type 2 (Th2) cytokines, which play an important role in the pathophysiology of allergic diseases, may have a role in antitumor immunity.³¹ Specifically, Th2 cytokines are involved in tumor surveillance by recruiting and activating eosinophils, macrophages, Type 2 CD8+ T cells, and natural killer cells, all of which may attack tumor cells. Other cytokines derived from Th2 cells also have anti-tumor properties. For instance, tumor necrosis factor α (TNF α) has a direct antitumor cytotoxic effect.³² Additionally, interleukin (IL)-4 may inhibit angiogenesis, and IL-10 may reduce inflammation-associated carcinogenesis. Other potential mechanisms underlying the immune surveillance theory include: (*i*) diminished B-cell response resulting from IgE binding to its lower affinity receptor (CD23) and preventing release of soluble CD23 and (*ii*) reduced Type 17 helper T cell cytokine secretion in persons with allergies.³³ Although an exact mechanism by which atopic conditions may be protective against childhood RMS is unknown, the immune surveillance theory is a plausible candidate.

Our study must be considered in the light of certain limitations. As with any case-control study, there is the potential for recall bias. In other words, it is possible that mothers of case children may differentially report exposures or health histories. In relation to allergies, some have speculated that mothers of controls may be more likely to report a history of allergies compared to mothers of cases because case mothers may minimize the importance of other health conditions in the presence of their child's cancer diagnosis.³³ However, it is also possible that the opposite may occur, whereby case mothers are more likely to accurately report a history of health conditions. It is impossible to determine if recall bias played a role in this assessment; however, our results are con-

sistent with previous reports of allergy and cancer.^{13,14} Although we adjusted for household income and parental education, there may be residual confounding due to socioeconomic status, as these factors are associated with atopic conditions and also appear to differ between RMS cases and controls in our population.^{23,25,34,35} Additionally, as the prevalence of atopic conditions has changed over time, this may limit the interpretation of these results due to the age of the study.^{25,36} We were not able to evaluate associations by tumor site or chromosomal translocation status, but we did assess effect heterogeneity by histologic subtypes (*i.e.*, embryonal and alveolar).³ This enabled us to evaluate differing effects of these exposures on disease risk by subtype. Although this is a relatively older study, with dates of diagnosis and enrollment from April 1982 to July 1988, parents were interviewed at the time of diagnosis (or enrollment for controls).^{7,8,10} Furthermore, this is the largest case-control study of childhood RMS, which is an important consideration as very little is known about the epidemiologic characteristics of this malignancy.

In conclusion, our findings suggest that allergies, atopy and risk factors for atopic conditions are inversely associated with childhood RMS. These findings are consistent with the association between allergies and childhood ALL and is supported by the immune surveillance theory. As several of these characteristics are more broadly related to immune system development, these findings point towards a possible role of immunity in the etiology of RMS. To our knowledge, this is the first assessment of its kind in the largest case-control study of childhood RMS; however, these findings must be validated in an independent population. Furthermore, additional work is needed to characterize the biological basis of this association. Future studies evaluating genetic and epigenetic profiles associated with allergies and atopy may be important in disentangling these effects. Additionally, novel study designs and methodologies are needed to evaluate these questions. Ultimately, we hope that the identification of risk factors for childhood RMS will lead to new cancer prevention strategies.

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