Parental Military Service, Agent Orange Exposure, and the Risk of Rhabdomyosarcoma in Offspring

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Objective To evaluate the role of parental military service-related exposures and rhabdomyosarcoma (RMS) risk in offspring using data from a large case-control study of childhood RMS.

Study design Cases (n = 319) were enrolled from the third trial run by the Intergroup Rhabdomyosarcoma Study Group. Population-based controls (n = 319) were pair-matched to cases on race, sex, and age. Conditional logistic regression was used to evaluate parental military service-related exposures and their associations with childhood RMS by generating aORs and 95% CIs. Statistical significance was defined as $P < .05$.

Results There were no significant associations between parental military service and childhood RMS. The strongest association was with maternal military service; however, this association was attenuated and did not remain significant after adjusting for covariates (aOR = 2.75, 95% CI 0.71, 10.62). An elevated effect estimate was found when assessing paternal exposure to Agent Orange (AO) and childhood RMS but was not statistically significant (aOR = 1.72, 95% CI 0.55, 5.41).

Conclusions We found little evidence that parental military service of AO exposure influences the risk of RMS in offspring. These findings are notable in light of the continuing controversies surrounding the intergenerational effects of AO exposure. *(J Pediatr 2014;165:1216-21)*.

Rhabdomyosarcoma (RMS) is a rare, highly malignant tumor of primitive mesenchymal cells that display muscle differentiation, which can occur anywhere in the body. Although RMS is the most common soft tissue sarcoma in children and adolescents <20 years of age in the US, there are only about 350 new cases of RMS diagnosed per year.[1] Because of the rarity of these tumors, relatively little is known about the etiology and epidemiology of childhood RMS. A small percentage of cases (~5%) are associated with mutations in *TP53* (Li-Fraumeni syndrome), *HRAS* (Costello syndrome), and *NF1* (neurofibromatosis type 1) genes.[2-4] Previous reports have identified a few positive associations between potential risk factors and childhood RMS, including prenatal radiograph exposure,[5] maternal drug use,[6] advanced maternal age,[7] large for gestational age at birth,[7] and birth defects.[8] However, these associations have largely not been replicated. In addition, parental environmental exposures including paternal smoking, maternal exposure to various chemicals, and diets that include organ meats, have been suggested as potential risk factors for childhood RMS.[9-11] Much work remains in identifying novel associations.

During the Vietnam War, US military forces sprayed millions of gallons of Agent Orange (AO) and other herbicides on lands in Vietnam, Laos, and other nearby areas to remove forest cover, destroy crops, and clear vegetation from the perimeters of US bases.[12] This effort, known as Operation Ranch Hand, lasted from 1962 to 1970. There is suggestive evidence that the risk of birth defects (specifically spina bifida) is increased among the offspring of US soldiers who were exposed to AO.[12,13] In addition, certain cancers in adulthood, including some soft tissue sarcomas, are associated with military service-related exposure to AO or other herbicides.[12] However, according to the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides, there is inadequate or insufficient evidence to determine if there is an association between parental exposure to AO and childhood cancers.[12,14]

Although studies related to parental AO exposure and cancer in offspring have been largely inconclusive,[12,14] to our knowledge, there have been no direct assessments of the association between parental military service, AO exposure, and the risk of RMS in children. Because of lingering questions related to parental AO exposure and childhood cancer, we evaluated these associations in a large case-control study of childhood RMS.

2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4-D	2,4-dichlorophenoxyacetic acid
AO	Agent Orange
IRS-III	Intergroup Rhabdomyosarcoma Study
RMS	Rhabdomyosarcoma

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Methods

Cases and controls were enrolled in a trial previously coordinated by the Intergroup Rhabdomyosarcoma Study (IRS-III) group.[15] The details regarding the case-control study have been previously described.[5,6,8] In summary, the cases were consecutively enrolled in the IRS-III study at the time of their RMS diagnosis from April 1982 to July 1988 and were recruited from 69 hospitals across 46 states and the District of Colombia. Eligibility criteria for study enrollment of cases included being diagnosed with RMS at 20 years of age or younger, speaking English or Spanish, receiving treatment at an institution where Institutional Review Board approval was obtained, having a home telephone, and being a US citizen. Of the 511 patients with childhood RMS 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, 9 were not US citizens, 15 were from families that did not speak English or Spanish, and 18 were treated in institutions where the Institutional Review Board did not approve the study. An additional 89 cases did not participate because of parental (n = 41) or physician (n = 30) refusal, and 18 families could not be located. Seventy-three percent (n = 322) of eligible cases were interviewed and matched with controls; controls were not identified for the remaining 29 eligible cases with completed interviews, and, therefore, these cases were excluded from this assessment.[5,6,8] Of those interviewed, 319 eligible cases had available information on parental occupation.

Controls were identified by random-digit dialing during the same period.[5,6,8] Specifically, the telephone area code and first 5 digits of the cases' phone number were used with 2 randomly selected terminal digits to search for matching controls. Controls were matched to cases on race, sex, and age (within 1 year for cases aged 0-5 years at diagnosis, and within 3 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.[5,6,8]

The Institutional Review Board at the Baylor College of Medicine approved this study. Informed consent was obtained from the parents or guardians of each of the case and control children.

Data were collected from case and control families by telephone interview 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 (6 case families and 2 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 8-9 years prior to the interview. The questions pertaining to military service, however, focused on the period of the Vietnam War (9-25 years prior to the interview). Each parent was asked if he/she ever served in the armed forces before the date of the index child's diagnosis and, if so, to specify between which years the service occurred. Each parent was also asked if he/she was in contact with nuclear, chemical, and biological weaponry, radiation, radar or microwaves, or AO.

Covariates for this analysis were selected a priori and included total annual household income (categorized as <$20 000, $20 000-$39 999, ≥$40 000); length of pregnancy (categorized as preterm, term, or post-term); maternal spotting, cramping, or abnormal bleeding during index pregnancy (yes or no); maternal and paternal educational level (total number of completed years); and recreational drug use during the year prior to index child's birth (yes or no). All statistical models were adjusted for these covariates as well as the matching factors including the child's sex (male or female), age at diagnosis (in years), and race (categorized as White, Black, or other).

Statistical Analyses

Descriptive statistics were used to characterize the demographic variables among the case and control groups. Frequency distributions were tabulated for categorical variables, and means and SDs were calculated for continuous variables. Univariable regression models were used to evaluate differences in potential confounders, including demographic and pregnancy-related characteristics, between cases and controls; statistical significance was tested using χ^2 tests for categorical variables and 2-sided t tests for continuous variables. Conditional logistic regression was used to evaluate parental military service and service-related exposures and their associations with childhood RMS by generating aORs, 95% CIs, and P values. An association was considered statistically significant if $P < .05$. Military service-related chemical exposures were included only if they occurred prior to the child's birth and included AO, radiation, radar or microwaves, nuclear weaponry, chemical weaponry, or biological weaponry. All analyses were performed using SAS v 9.2 (SAS Institute, Cary, North Carolina).

Results

There were 319 patients with RMS and 319 pair-matched controls available for the present analysis. Demographic and pregnancy-related characteristics of patients with RMS and controls are presented in **Table I**. Patients with RMS and controls were largely similar on demographic characteristics, other than total annual family income, for which a significantly higher proportion of case families were in the lowest income category (32.8% of cases vs 23.9% of controls, $P = .02$). Cases and controls did differ on pregnancy-related characteristics including: (1) length of pregnancy (preterm births were more

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