Cancer Risk and Parental Pesticide Application in Children of Agricultural Health Study Participants

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Parental exposure to pesticides may contribute to childhood cancer risk. Through the Agricultural Health Study, a prospective study of pesticide applicators in Iowa and North Carolina, we examined childhood cancer risk and associations with parental pesticide application. Identifying information for 17,357 children of Iowa pesticide applicators was provided by parents via questionnaires (1993–1997) and matched against the Iowa Cancer Registry. Fifty incident childhood cancers were identified (1975–1998). Risk of all childhood cancers combined was increased [standardized incidence ratio (SIR) = 1.36; 95% confidence interval (CI), 1.03–1.79]. Risk of all lymphomas combined was also increased (SIR = 2.18; 95% CI, 1.13–4.19), as was risk of Hodgkin’s lymphoma (SIR = 2.56; 95% CI, 1.06–6.14). We used logistic regression to explore associations between self-reported parental pesticide application practices and childhood cancer risk. No association was detected between frequency of parental pesticide application and childhood cancer risk. An increased risk of cancer was detected among children whose fathers did not use chemically resistant gloves [odds ratio (OR) = 1.98; 95% CI, 1.05–3.76] compared with children whose fathers used gloves. Of 16 specific pesticides used by fathers prenatally, ORs were increased for aldrin (OR = 2.66), dichlorvos (OR = 2.06), and ethyl dipropylthiocarbamate (OR = 1.91). However, these results were based on small numbers and not supported by prior biologic evidence. Identification of excess lymphoma risk suggests that farm exposures including pesticides may play a role in the etiology of childhood lymphoma. Key words: agricultural workers, cancer, children, occupational exposure, pesticides. Environ Health Perspect 112:631–635 (2004). doi:10.1289/ehp.6586 available via http://dx.doi.org/[Online 22 December 2003]

Despite advances in treatment, cancer remains a leading cause of childhood mortality (Ries et al. 1999), and its etiology remains poorly understood (Chow et al. 1996). Exposure to pesticides has been implicated as a possible contributing factor in the pathogenesis of childhood cancer (Daniels et al. 1997; Zahm and Ward 1998), and several pesticides are carcinogenic in bioassays [International Agency for Research on Cancer (IARC) 1986]. In two reviews (Daniels et al. 1997; Zahm and Ward 1998), parental pesticide use was fairly consistently associated with acute lymphocytic leukemia and central nervous system tumors, the two most common childhood cancers, and less consistently with Wilms tumor, Ewing’s sarcoma, and soft-tissue sarcomas.

Associations between parental pesticide use and childhood cancer risk have been linked to either the mother or father. Evidence from animal models suggests that exposure of the father during the preconception period may be especially important (Buckley 1994). Although not well investigated, critical time windows for childhood carcinogenesis may include the preconception, intrauterine, and postnatal periods (Anderson et al. 2000; Olshan et al. 2000). Several previous studies have examined the relationship of paternal pesticide exposure to childhood cancer by using paternal occupation in farming as a proxy for pesticide use (Gold et al. 1982; Hemminki et al. 1981; Kristensen et al. 1996; Magnani et al. 1990; Roman et al. 1993). However, inferring pesticide exposure from paternal occupation can be an imprecise measure of exposure assessment (Gold and Sever 1994). Most previous studies of pesticides and childhood cancer lack detailed information on the frequency of specific pesticide exposures, on the nature of job tasks involving pesticides, and on the possible effect of pesticide protection practices (Daniels et al. 1997; Olshan and Daniels 2000).

The Agricultural Health Study (AHS), a large, prospective cohort of licensed pesticide applicators and their families in Iowa and North Carolina, was designed to examine the relationship of pesticide exposure to adult chronic diseases and has assembled detailed information on pesticide use by farmers and their spouses (Alavanja et al. 1996). In this report, we examine cancer risk among children of pesticide applicators and draw upon the detailed pesticide exposure data provided by AHS participants to explore the relationship of childhood cancer risk to parental pesticide application practices, including specific chemical use, frequency of exposure, and protective practices employed.

Materials and Methods

The AHS is a collaborative effort of the National Cancer Institute, the National Institute of Environmental Health Sciences, and the U.S. Environmental Protection Agency. The design of the AHS is discussed in detail elsewhere (Alavanja et al. 1996). Briefly, it is a large prospective study of certified pesticide applicators and their spouses in Iowa and North Carolina. Persons applying for pesticide application licenses between 1993 and 1997 in North Carolina and Iowa were asked to participate in the study. Both private pesticide applicators (largely farmers) and commercial pesticide applicators (Iowa only) were enrolled. These analyses are limited to private pesticide applicators (farmers) because information about children was collected only from private applicators’ spouses. Approximately 82% of eligible private pesticide applicators (n = 52,395) were enrolled (Gladen et al. 1998). At enrollment, pesticide applicators were asked to complete a questionnaire providing information on pesticide application practices and health-related behaviors, and additional details on pesticide use and work practices were obtained from take-home questionnaires. Spouses were enrolled through a questionnaire brought home by the licensed applicator or by telephone. Females (applicants and spouses; n = 20,625) were also asked to complete a questionnaire on female and family health that collected information on children born during or after 1975, for manuscript review, and the Iowa and North Carolina Field Stations and Cancer Registries. We thank S. Long for data management, L. Margolis for manuscript review, and the Iowa and North Carolina Field Stations and Cancer Registries. The study was funded by the intramural programs of the National Institute of Environmental Health Sciences (NIEHS), the National Cancer Institute, and the U.S. Environmental Protection Agency, and grant P30 ES05605 from the NIEHS. The authors declare they have no competing financial interests. Received 11 July 2003; accepted 22 December 2003.
including names, dates of birth, and social security numbers. A total of 21,375 children born during or after 1975 were enumerated by their mothers. Of these children, 17,357 (81%) resided in Iowa and 4,018 (19%) resided in North Carolina. A subsequent linkage of mothers and fathers to Iowa birth certificates indicated that the enumeration of children via questionnaires was accurate, because 95% of these children were verified through birth certificate linkage (Romiti P, personal communication).

We used a hybrid study design, in which the prospective cohort of pesticide applicators was formed between 1993 and 1997, and cancer cases among their children were both retrospectively and prospectively identified after parental enrollment. Identifying information for children in Iowa was matched against the Iowa Cancer Registry to identify cases of childhood cancer arising between 1975 and 1998. Childhood cancer was defined as cancer diagnosed from birth through 19 years of age, which conformed with the standard SEER (Surveillance, Epidemiology, and End Results) childhood cancer classification (Ries et al. 1999). Through this linkage, 50 cancers in children of AHS participants 0–19 years of age were identified; 37 cases were a perfect match, and the remaining 13 cases were matched on name and birth date and verified using birth certificate and driver’s license databases.

A similar linkage was performed with the North Carolina Central Cancer Registry for 1990–1998. The starting point was later in North Carolina because the cancer registry was not fully operational until 1990. A matching algorithm based on names, dates of birth, and social security numbers initially identified six cancer cases among North Carolina children between 0 and 19 years of age. Two of these cases were subsequently excluded because they were not invasive malignancies; the remaining four were leukemia, brain tumors, and bone tumors. Because of the small number of North Carolina cases, subsequent analyses were restricted to Iowa children.

A standardized incidence ratio (SIR) was generated to compare the observed number of childhood cancer cases identified among children of AHS participants to the expected number. The expected number of cancer cases was generated by applying age, sex, race, and time-period–specific childhood cancer rates from Iowa SEER data to the person-years contributed by eligible children in the sample, according to the method of Breslow and Day (1987).

Pesticide exposure data were obtained from self-reports by applicators and spouses. The questionnaires are available in electronic format (Agricultural Health Study Data Working Group 2002). We focused on parental pesticide mixing and application, because these tasks are associated with potentially high exposure. General questions included whether applicators personally mixed and applied pesticides (ever/never), frequency of pesticide mixing and application (days per year), and whether they personally mixed and applied pesticides > 50% of the time when pesticides were used or required mixing (yes/no). Information on ever use of 50 specific pesticides was obtained via the enrollment questionnaire. Detailed exposure information (decade of first use, and frequency and duration of use) was solicited for 22 pesticides in the initial questionnaire, and for 28 additional pesticides in the take-home questionnaire. Applicators’ responses regarding decade of first use and duration of use were used to create dichotomized exposure variables that indicated whether each specific pesticide had been used before the child’s birth. Children for whom timing of use was missing were excluded from this analysis. Individual pesticides were treated as separate exposure variables in the analysis when there were five or more exposed cases. Individual pesticides were also grouped into classes (organophosphates, organochlorines, carbamates, chlorphenoxyl compounds, and pyrethroids) to create exposure variables based on potentially similar mechanisms of pesticide action. Applicators were also asked to indicate whether they generally used protective equipment, such as chemically resistant gloves, during pesticide application.

Although fathers were the primary licensed applicators in most households, mothers were also asked about mixing and application of pesticides (ever/never), and frequency and duration of pesticide mixing and application. Mothers were asked about mixing and application of 50 different individual pesticides, but they were not asked to provide information about timing, frequency, or duration of use for individual pesticides. For 17,280 children, the father was the primary licensed pesticide applicator. For 76 children, including one cancer case, the mother was the licensed pesticide applicator. Therefore, when the mother was the applicator, her data were more detailed than those of the remaining mothers, whereas the father’s data were less detailed than those of most fathers who were applicators. This made it difficult to combine data for children whose mothers were applicators with that for children whose fathers were applicators. The 76 children whose mothers were licensed applicators were therefore eliminated from analyses of specific parental exposures. Although mothers who were applicators had potentially higher levels of exposure, there were too few of them for a stand-alone analysis.

Logistic regression analyses were used to compute odds ratios (ORs) and 95% confidence intervals (CI), using SAS software (version 8; SAS Institute, Cary, NC, USA) to examine the association between pesticide exposure variables and childhood cancer. Multiple logistic regression models were also created to examine potential confounders of cancer risk. Parental age at child’s birth, child’s sex, child’s birth weight, history of parental smoking (ever/never), paternal history of cancer, and maternal history of miscarriage were explored as potential additional confounders in bivariate analyses, but were not significant and were excluded from final models. Race of child was not explored as a potential confounder because the sample included very few nonwhite children. Child’s age at parent’s enrollment in the study was related to cancer risk ($\beta$ coefficient = 0.06; $p = 0.02$) and was included in final models.

The AHS and linking of AHS data with the Iowa and North Carolina Cancer Registries were approved by the Institutional Review Boards of the National Cancer Institute, the National Institute of Environmental Health Sciences, the University of Iowa, and Battelle.

Results

Children of AHS participants were predominantly white, with slightly fewer females than males (Table 1). In Iowa, most farms on which children reside produce grains and livestock, with field corn as the most common farm product. Most children were between 5 and 19 years of age at the time of study enrollment. Mean maternal and paternal age at enrollment was 39 and 41 years, respectively.

SIRs were generated only for Iowa ($n = 50$) because of the small number of cases in North Carolina ($n = 4$). The expected total number of cancer cases in Iowa was 37, yielding an SIR of

| Table 1. Demographic characteristics of 17,357 children $a$ of Iowa participants in the Agricultural Health Study. |
|-----------------------------------------------|
| No. (%)                                      |
|-----------------------------------------------|
| Sex                                           |
| Female                                       | 8,082 (48) |
| Male                                         | 8,659 (52) |
| Race                                         |
| White                                        | 16,439 (96) |
| Nonwhite                                     | 769 (4)   |
| Child’s age at enrollment (years)$b$          |
| < 5                                          | 3,182 (19) |
| 5–9                                          | 3,795 (22) |
| 10–14                                        | 4,568 (26) |
| 15–19                                        | 3,795 (22) |
| > 19                                         | 1,929 (11) |
| Major farm crops/livestock$^c$                |
| Field corn                                    | 15,811 (92) |
| Soybeans                                     | 14,416 (84) |
| Hogs                                         | 9,528 (55) |
| Beef                                         | 7,791 (45) |
| Hay                                          | 6,700 (39) |
| Alfalfa                                      | 5,977 (35) |
| Oats                                         | 5,364 (31) |

$^a$Children born during/after 1975; columns may sum to < 17,357 due to missing data. $^b$Child’s age at parent’s enrollment in 1993–1997. $^c$Farm type by crop product; total > 100% because most farms produce multiple products.
1.36 (95% CI, 1.03–1.79). When tumor-specific SIRs were generated, more lymphoma cases were observed (n = 9) than expected (SIR = 2.18; 95% CI, 1.13–4.19). More cases were also observed than expected for brain tumors (SIR 1.60; 95% CI, 0.89–2.89), neuroblastoma (1.26; 95% CI, 0.40–3.89), retinoblastoma (SIR = 1.63; 95% CI, 0.41–6.53), Wilms tumor (SIR = 1.56; 95% CI, 0.50–4.84), and bone tumors (SIR = 2.19; 95% CI, 0.82–5.84), but there were small numbers of these tumors.

SIRs for individual lymphoma subtypes were also examined. An increased incidence of Hodgkin’s lymphoma was observed (SIR = 2.56; 95% CI, 1.06–6.14). Increased incidences of Burkitt’s lymphoma (SIR = 2.67; 95% CI = 0.37, 19.0) and non-Hodgkin’s lymphoma (SIR = 1.18; 95% CI = 0.29, 4.70) were observed, but few cases of these tumor types were present (Table 2).

Because of the small number of cancer cases identified, results of exposure analyses are presented only for factors involving five or more exposed cases (Table 3). All fathers reported applying pesticides, 72% reported mixing them personally more than 50% of the time, and 77% reported applying pesticides personally more than 50% of the time that they were used on the farm. No difference in cancer risk was observed for children whose fathers personally mix pesticides > 50% of the time, compared with those whose fathers personally mix < 50% of the time (OR = 1.02; 95% CI, 0.51–2.06). Cancer risk was similar for children whose fathers personally apply pesticides > 50% of the time, compared with children whose fathers apply pesticides < 50% of the time (OR = 0.74; 95% CI, 0.37–1.51). No relationship was detected between paternal frequency of application and childhood cancer (p = 0.12). When use of protective equipment was examined, children of fathers who reported that they generally did not wear chemically resistant gloves (16%) had a 2-fold excess risk of childhood cancer (OR = 1.98; 95% CI, 1.05–3.76). Of the 49 children who developed cancer, 47 had fathers who initiated pesticide application before the child’s cancer diagnosis date; data on date of initial pesticide application were missing for the remaining two children’s fathers.

Table 2. SIRs for cancers diagnosed < 17 years of age among 17,357 children of Iowa participants in the Agricultural Health Study, 1975–1998.

Table 3. Paternal pesticide mixing and application characteristics and risk of childhood cancer (1975–1998) among 17,280 children of Iowa participants in the Agricultural Health Study.
Daniels et al. 1997; Kristensen et al. 1996; Shu et al. 1988; Zahm and Ward 1998). Previous studies have most consistently implicated pesticide exposure in leukemia (Buckley et al. 1989), central nervous system tumors (Daniels et al. 1997; Zahm 1999), and neuroblastoma (Daniels et al. 2001). Our study did not detect an increased risk of these tumor types but did suggest an increase for childhood lymphoma.

Few studies have previously examined risk of childhood lymphoma in association with pesticide exposure (Kristensen et al. 1996; Leiss and Savitz 1995; Schwartzbaum et al. 1991). Increased risk of non-Hodgkin’s lymphoma in association with paternal or maternal pesticide exposure was previously reported (Kristensen et al. 1996; Leiss and Savitz 1995), but associations have not been reported for Hodgkin’s disease (Kristensen et al. 1996; Schwartzbaum et al. 1991). In adult studies, pesticide exposure has been more frequently implicated in non-Hodgkin’s lymphoma (Dich et al. 1997; Persson 1996), although a few studies have also suggested an association with Hodgkin’s lymphoma (Hardell et al. 1981; Persson et al. 1989, 1993). Adult epidemiologic studies have specifically implicated organochlorines (Hardell et al. 2001; IARC 1991), organophosphorus compounds (Cantor et al. 1992; Zahm et al. 1990), and phenoxy herbicides (Hoar et al. 1986; Zahm and Blair 1992; Zahm et al. 1990) in excess lymphoma risk. A recent study of children of pesticide applicators in Sweden also described an increased risk of Hodgkin’s lymphoma (Dich et al. 1997; Persson et al. 1989, 1993).

Table 4. Maternal pesticide mixing and application characteristics and risk of childhood cancer (1975–1998) among 17,280 children of Iowa participants in the Agricultural Health Study.

| Mix/apply pesticides personally | No. exposed (%) | No. exposed cases | OR* (95% CI) |
|--------------------------------|-----------------|------------------|-------------|
| Yes                            | 6,591 (38)      | 22               | Referent    |
| No                             | 9,974 (58)      | 26               | 0.73 (0.41–1.29) |

Frequency of mixing/application (days/year)

| None                          | 6,591 (38)      | 22               | Referent    |
| < 5                           | 3,799 (22)      | 4                | 0.30 (0.10–0.86) |
| 5–19                          | 2,761 (16)      | 9                | 0.90 (0.42–1.95) |
| > 19                          | 587 (3)         | 3                | 1.41 (0.42–4.72) |

*Adjusted for child’s age at enrollment.

Table 5. Parental use of specific pesticides* and subsequent childhood cancer risk among 17,280 children of Iowa participants in the Agricultural Health Study.

| Maternal use* (ever) | No. exposed (%) | No. exposed cases | OR* (95% CI) |
|----------------------|-----------------|------------------|-------------|
| Chlorophenoxy herbicides | 3,189 (19)      | 7                | 0.67 (0.30–1.49) |
| Organophosphate insecticides | 4,259 (25)      | 14               | 1.10 (0.59–2.07) |
| 2,4-D                | 3,009 (17)      | 7                | 0.72 (0.32–1.60) |
| Glyphosate           | 6,075 (35)      | 13               | 0.61 (0.32–1.16) |
| Malathion            | 3,273 (19)      | 11               | 1.12 (0.57–2.20) |

*Includes chlorpyrifos, coumaphos, diazinon, dichlorvin, fonofos, malathion, parathion, phorate, terbufos, and trichlorfon.

Although power was limited for many detailed exposure analyses, we did detect an association between paternal prenatal exposure to aldrin and childhood cancer. This could be a chance finding, because recent reviews have suggested that aldrin is unlikely to have significant carcinogenic potential (IARC 1987; Sielken et al. 1999; Stevenson et al. 1999). This finding should be interpreted with caution given the lack of evidence of carcinogenicity,
and lack of associations between other specific pesticide exposures and childhood cancer in our study.

The finding of an increased risk of childhood cancer associated with lack of chemically resistant glove use by the father deserves attention. Lack of glove use could reflect direct exposure to pesticides to the applicator (Rutz and Krieger 1992) and indirectly to children. Alternatively, lack of glove use could be a marker for less meticulous chemical practices in general, which could increase the opportunity for exposure to children on the farm. Such behavior has been associated with an increased risk of high-pesticide-exposure events (Alavanja et al. 2001) and thus may also be an indicator of less cautious handling of pesticides.

In conclusion, our study detected a small increase in risk of all childhood cancers combined, and lymphomas specifically, in a pesticide-exposed agricultural population. Our data suggest a modest increase in cancer risk among children of men who apply pesticides but do not use chemically resistant gloves, and among children of men who use aldrin before conception. The finding of increased lymphoma risk warrants further exploration in future studies, with improved understanding of pesticide exposure during critical time periods, and attention to exposure to specific chemical classes and other farm exposures.

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