Gliomas and Farm Pesticide Exposure in Men: The Upper Midwest Health Study

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ABSTRACT. The National Institute for Occupational Safety and Health evaluated farm pesticide exposure and glioma risk in a study that included 457 glioma cases and 648 population-based controls, all adult men (18–80 yr old) and nonmetropolitan residents of Iowa, Michigan, Minnesota, and Wisconsin. Multiple logistic regressions were used to control for farm residence, age, age group, education, and exposure to other pesticides. No associations were found between glioma and 12 specific pesticides. We estimated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) and found reduced glioma risk for insecticides (OR = 0.53, CI = 0.37–0.77), fumigants (OR = 0.57, CI = 0.34–0.95), and organochlorines (OR = 0.66, CI = 0.47–0.94). In analyses excluding proxy respondents (47% of cases) most CIs included 1.0. No positive association of farm pesticide exposure and glioma was found. Other farm exposures may explain the excess brain cancer risk seen in previous studies.
<Key words: agricultural workers' diseases, case-control studies, glioma, pesticides, rural population>

FARMERS EXPERIENCE a lower overall cancer mortality than the general population. However, several studies have indicated that individuals working in agriculture had an excess risk of brain cancer ranging from 1.5 to 5.0;[1–7] although a few other studies have not found an increased risk.[8–10] Agricultural workers are exposed to a number of agents hypothesized to increase the risk of brain cancer, including pesticides, nitrates, solvents, and viruses. Reviews have explored the relationship between pesticides and cancer,[11–13] as well as the causes of neoplasms of the nervous system.[14–16] These studies focused predominantly on adult men who lived in rural areas, and there was no definitive evidence explaining the excess risk. Therefore, the National Institute for Occupational Safety and Health (NIOSH) initiated the Upper Midwest Health Study, an examination of brain cancer risk in the nonmetropolitan population.

Using a case-control design, this study evaluated associations between reported farm exposures and gliomas among nonmetropolitan residents in four upper midwestern states. The study focused on histologically confirmed primary intracranial gliomas, rather than all brain neoplasms, to reduce heterogeneity among the

case participants. We required that tumors be primary. A brain glioma was defined as a neoplasm arising from a glial cell and having an ICD-O code 938–948.[17]

The primary hypothesis was that pesticides increase glioma risk. This study examined similar numbers of men and women. Findings about associations between farm pesticide exposure and gliomas in women were reported separately.[18]

Materials and Method

Study sample and study design. The study sample and design were described previously.[18] Members of the Control group were stratified according to gender and 10-yr age groups. All men were residents of nonmetropolitan counties of 4 states on January 1, 1995, had a driver license or state identification card (those aged 18–64 yr), or were on the Health Care Financing Administration's Medicare data tape (those aged 65–80 yr). Individuals with a prior malignancy other than a glioma were included. Cases with a histologically confirmed primary intracranial glioma (ICD-O codes 938–948) diagnosed from January 1, 1995, through January 31, 1997, were identified through participating medical facilities and offices of neurosurgeon. Physician consent was obtained before contacting cases or their next of kin. This study was approved by the NIOSH Human Subjects Review Board (HSRB 94-DSHEFS-08) and review boards of all participating institutions.

We solicited participation with introductory letters and follow-up telephone calls. Respondents were asked to review 2 lists of pesticides, which were enclosed with a letter confirming the interview appointment. Pesticide toxicology and the quantity of the pesticides used in the 4 study states were the criteria for determining which pesticides would be included in the respondent prompt lists.[19] The questionnaire, modified from one developed by the National Cancer Institute,[20] included a farm section, asking about exposure to these specific pesticides. Direct pesticide use by the participant and living or working on a farm where pesticides were used were differentiated. When a proxy (surrogate) respondent was needed, we attempted to recruit a relative knowledgeable about farming and occupational histories (sometimes a spouse but usually a brother or son) for male participants.

Statistical analyses. The NIOSH pesticide reference database, which was expanded for this study from the pesticide lists sent to participants before the interviews, was used to associate trade name responses with the appropriate generic name(s) for our analyses. For example, Bronco®, Bullet®, Cannon®, Freedom®, Lariat®, Lasso®, and Saddle® would all link to alachlor. Pesticides were classified into groups based on chemical similarity.

We hypothesized that pesticide exposure would increase the risk for intracranial brain gliomas. In this study all estimates of association have been adjusted through stratification or modeling. Age-stratified odds ratios (ORs) and 95% confidence intervals (CIs) were first computed to determine whether hypothesized risk factors such as farm residence were associated with an increased odds ratio (CI does not include 1.0) for developing intracranial brain gliomas, and to assist in determining potential confounders of the associations of interest.[21] We used SAS 8.0 software for all analyses.[22] We ran unconditional multiple logistic regression models to obtain maximum-likelihood parameter estimates.[23] In these models we evaluated the effects of multiple exposures and confounders simultaneously. In each analysis of a pesticide group or an individual pesticide we included a categorical variable for any other pesticide exposure (on the farm, in the house and garden, or on a nonfarm job).

Because the participants' responses are not a true gold standard, correcting a proxy's responses toward the participant's responses may overcorrect.[24,25] We decided a priori not to make a statistical adjustment for the type of respondent. Instead, we performed separate analyses using data from participants only, and from participants and proxies combined.[26] In our analyses we used age on January 1, 1993 (the cutoff for exposure information used in the interviews), rather than age at interview, because many cases died before the interview, and because on average controls were interviewed earlier than cases. Adjustment for control and case age on the date of diagnosis of the case was not an option, because our controls were frequency matched rather than individually matched.

Results

There were 494 cases and 933 controls (all men) eligible to participate in the study. The final study sample included 457 cases (93% of those eligible) and 648 controls (70% of those eligible). Table 1 compares cases and controls for known demographic characteristics. Participating cases and controls differed significantly by age.

At the time of the interview, 270 case participants (59%) were alive and we interviewed 242, with (n = 77) or without (n = 165) the assistance of a relative or friend. We conducted proxy interviews for the 187 deceased case participants and 28 living case participants who were too ill to be interviewed in person. We interviewed a total of 47% of case participants by proxy only. We found a significant difference in mean participant age between case participants interviewed in person (mean = 46.2, CI = 44.3–48.1) and only by proxy (mean = 60.7, CI = 58.9–62.5). Most proxies were the participant's wife (56% of case proxies, 70% of control proxies), child or children (9%), sibling(s) (6%), parent(s) (4%), or a combination of these close relatives (23%).

Only 4 of 238 proxy interviews (2%) did not include a first-degree relative.

Controls were more likely than cases to report having lived on a farm where pesticides were used or animals were raised. These differences persisted in analyses adjusted for age, stratifying age group, education, and other pesticide exposure on the farm, in the house and garden, or on a nonfarm job (Table 2). In comparisons of broad categories of reported use of pesticides (herbicides, fungicides, insecticides, and fumigants), insecticides and fumigants were associated with a statistically significant decreased risk of glioma, as was the use of solvents or fuels to clean the hands after working on the farm (Table 2). When proxies were excluded, none were statistically significant. Farm acreage (results not shown) was not associated with risk of glioma.

The odds ratios of farm pesticide exposure are presented for major classes of pesticides, including and excluding proxy respondents (Table 3). We adjusted for age, stratifying age group, education, and other pesticide exposure on the farm, in the house and garden, or on a nonfarm job. Exposure to organochlorines was associated with a reduced risk of glioma. No other associations, some positive and some negative, were statistically significant. We found modest increased risks for exposure to carbamate fungicides and herbicides and dinitroanilines, although they were not statistically significant (Table 3).

The individual farm pesticides to which the most participants were exposed included 2,4-D (CAS 94-75-7); alachlor (CAS 15972-60-8); atrazine (CAS 1912-24-9); bentazon (CAS 25057-89-0); cyanazine (CAS 21725-46-2); DDT (CAS 50-29-3); diazinon (CAS 333-41-5); dicamba (CAS 1918-00-9); glyphosate (CAS 1071-83-6); imazethapyr (CAS 81335-77-5); malathion (CAS 121-75-5); metolachlor (CAS 51218-45-2); pendimethalin (CAS 40487-41-1); and trifluralin (CAS 1582-09-8). We observed no statistically significant associations in analyses including and excluding proxy respondents (results not shown; available from first author).

We compared cases and controls born on farms, especially farms reported by the respondents to have used pesticides later, with those who were not born on farms. We reasoned that farms on which pesticides were reported to have been used after a participant's birth were more likely to have had pesticides used before their birth (that is, during the pregnancy) as well. However, we saw no increased risk for participants born on farms (results not shown).

Discussion

This large study of histologically confirmed gliomas did not show an increased risk of glioma among those reporting having been exposed to or having used farm pesticides. Living on a farm and/or exposure to farm animals was indicated as a risk factor for brain cancer as early as the 1960s.[27] The strongest evidence for both farming and pesticide exposures as risk factors has come

Table 1.—Characteristics of Male Participants in the Upper Midwest Health Study

	Including Proxy Respondents				Excluding Proxy Respondents			
	Cases $n = 457$		Controls $n = 648$		Cases $n = 242$		Controls $n = 625$	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Age* group								
15–30	60	13	61	9	51	21	60	10
31–40	62	14	78	12	51	21	77	12
41–50	71	16	94	15	45	19	93	15
51–60	99	22	155	24	51	21	154	25
61–70	107	23	180	28	37	15	173	28
71–80	58	13	80	12	7	3	68	11
Ethnicity white non-Latino	448	98	633	98	236	98	610	98
Education								
college graduate	80	18	127	20	54	22	125	20
high school graduate	266	63	392	60	160	66	383	61
<12 years	91	20	129	20	28	12	117	19
Smoking history								
never smoked	183	40	219	34	115	48	214	34
ex-smoker	153	33	292	45	60	25	279	45
current (1993) smoker	121	27	137	21	67	28	132	21
Drinking alcohol ever	370	81	579	89	199	82	564	90

*Age on January 1, 1993. Eligibility requirement was age 18–80 at time of diagnosis (1995–1997) or control selection (1995).

Table 2.—Farm-related Practices and Risk of Gliomas among Men

	Including Proxy Respondents						Excluding Proxy Respondents					
	Cases $n = 457$		Controls $n = 648$				Cases $n = 242$		Controls $n = 625$			
Variable	*n*	%	*n*	%	OR	95% CI	*n*	%	*n*	%	OR	95% CI
Ever lived/worked on farm	294	64	440	70	0.86	0.66–1.11	149	62	423	68	0.93	0.67–1.29
Years on farm (among those ever on farm)												
<10	104	36	141	32	1.00	—	53	37	135	32	1.00	—
11–20	71	25	87	20	1.04	0.68–1.58	37	26	84	20	1.08	0.63–1.86
21–30	30	10	66	15	0.51	0.30–0.84	14	10	64	15	0.62	0.32–1.18
31–40	19	7	37	8	0.67	0.35–1.28	13	9	36	9	0.91	0.40–2.06
41–50	13	5	31	7	0.84	0.42–1.67	7	5	30	7	1.39	0.60–3.25
>50	50	17	77	18	0.84	0.53–1.33	20	14	73	17	1.08	0.56–2.10
Herbicides ever used	123	47	204	52	0.89	0.63–1.26	74	58	200	52	1.51	0.92–2.48
Insecticides ever used	139	54	276	70	0.53	0.37–0.77	80	63	271	71	1.09	0.64–1.88
Fungicides ever used	24	9	43	11	0.93	0.54–1.60	15	12	43	11	1.27	0.65–2.48
Fumigants ever used	23	9	62	16	0.57	0.34–0.95	18	14	61	16	1.02	0.56–1.87
On farm as adult (age 18+)	171	66	285	72	0.78	0.55–1.11	90	71	277	73	1.11	0.69–1.81
Cattle, hogs, chickens raised?†	140	82	270	95	0.24	0.12–0.46	71	79	263	95	0.21	0.09–0.46
Solvents to clean hands?†	79	46	168	59	0.58	0.40–0.86	48	53	166	60	0.66	0.40–1.10
Laundered pesticide-applicator clothes?†	11	9	23	9	0.79	0.36–1.73	7	11	22	9	0.80	0.31–2.08
Pesticides stored in house?†	10	9	15	6	1.62	0.69–3.79	4	6	15	6	0.66	0.40–1.10

*Adjusted for age, 10-year age group, education, farm residence.
†Only asked of participants who lived or worked on a farm after age 18. OR among this group.

Table 3.—Exposure to Categories of Farm Pesticides and Risk of Glioma in Men

		Including proxy respondents				Excluding proxy respondents			
Category	IARC*	Cases $n = 457$	Controls $n = 648$	OR	95% CI	Cases $n = 242$	Controls $n = 625$	OR	95% CI
No pesticide exposure (farm, home, job)		128	128			79	117		
Arsenicals	H-1; A-I,-L	15	33	0.73	0.39–1.39	9	31	1.27	0.57–2.82
Benzoic acids		40	60	1.08	0.70–1.67	21	59	1.08	0.62–1.90
Carbamates	H-2B; A-S,-L	40	67	0.98	0.64–1.50	22	66	1.13	0.66–1.96
C insecticides		31	55	0.91	0.69–1.20	18	54	1.17	0.65–2.12
C herbicides		18	21	1.42	0.74–2.73	10	21	1.43	0.64–3.20
C fungicides		4	5	1.33	0.35–5.02	3	5	2.22	0.50–9.93
Chloroacetanilides		50	79	1.02	0.68–1.52	25	77	0.95	0.56–1.59
Dinitroanilines	A-L	42	54	1.29	0.83–2.01	19	53	1.05	0.58–1.88
Inorganics	H-1; A-S,-L,-I	9	21	0.45	0.19–1.09	7	21	0.58	0.21–1.59
Organochlorines	H-2A,-2B; A-S,-L,-I	67	146	0.66	0.47–0.94	34	142	0.76	0.48–1.21
Organophosphates	H-2B; A-S,-L,-I	72	140	0.75	0.54–1.06	39	136	0.87	0.56–1.35
OP insecticides		62	123	0.76	0.53–1.08	34	120	0.89	0.56–1.42
OP herbicides		46	66	1.13	0.74–1.71	22	64	0.98	0.57–1.70
Phenoxys	H-2B; A-I	67	121	0.87	0.61–1.24	43	120	1.36	0.88–2.12
Triazines	H-2B; A-S,-L	71	127	0.86	0.61–1.22	36	125	0.96	0.62–1.51
Urea-based	A-L	13	19	1.11	0.53–2.29	9	18	1.78	0.76–4.18
Estrogenic		86	152	0.87	0.62–1.21	43	148	0.90	0.58–1.39

*International Agency for Research on Cancer carcinogenicity evaluations for humans (H-1 definite, H-2A probable, H-2B possible, H-3 insufficient information) and animals (A-ES evidence suggesting lack of carcinogenicity, A-I inadequate evidence, A-L limited evidence, A-S sufficient evidence).
†Adjusted for age, 10-year age group, education, and any other/no other pesticide exposure on the farm, in the house and garden, or on a nonfarm job.

from case-control studies. For farmers, several studies showed elevated risks of brain cancer.[4-7,28,29] However, a farm exposure responsible for the increase has not been identified.

Reports on associations between brain cancer and farm pesticide exposure in men, provided by cohort and nested case-control studies of farmers and pesticide applicators (many of whom were also farmers), ecological studies, and case-control studies of brain cancer have not been consistent. Studies of pesticide applicator cohorts have reported brain cancer risks ranging from half those in the general population to three times as great; statistically significant results almost always were restricted to those over age 65 yr.[10,30-43] Three case-control studies and one ecological study found a positive statistical association between farm pesticide exposure and glioma incidence.[6,44-46] Several studies showed elevated levels of chromosomal aberrations in pesticide-exposed workers.[47,48] In nearly all of these studies the range of pesticides used and extent of pesticide exposure were not available. Most did not specify tumor type; however, gliomas are the most common tumors, and men, the focus of most pesticide studies, have a higher incidence of glioma than women do.[49] A review of the literature on brain cancer and pesticide exposure concluded that "the results of retrospective case-control studies are conflicting," and that the data were insufficient to assume a causal relationship between pesticide exposure and brain cancer (p. 110).[13] Some recent studies[8,9,50] did not find a positive association between pesticide exposure and glioma incidence.

Many pesticides in the categories in Table 3 have been characterized by the International Agency for Cancer Research (IARC) as probable (Group 2A) or possible (Group 2B) human carcinogens. Arsenicals and some of the inorganic pesticides are known human carcinogens (Group 1). IARC has also reported limited (L) or sufficient (S) evidence that many pesticides, including some carbamates, organochlorines, organophosphates, and triazines, are carcinogenic in animals (see Table 3). However, none of the pesticides identified as carcinogenic in animal studies have been associated with glioma in animals.[51] Our analyses showed that reported exposure to farm pesticides characterized by IARC as potentially carcinogenic was not associated with increased risk of glioma.

A chemical must cross the blood-brain barrier to exert carcinogenic potential in the brain, either by transport through endothelial and glial cell membranes or, if lipophilic and not highly protein bound, by active transport into the brain.[52,53] The association of parkinsonism and Parkinson's disease with occupational exposure to pesticides[54,55] suggests that pesticides may cross the blood–brain barrier. Other pesticides may alter the permeability of the blood-brain barrier. For example, combined exposure to DEET (N,N-diethyl m-toluamide) and permethrin was reported to disrupt the blood-brain barrier in rodents.[56]

Insecticides in the organochlorine, organophosphate, and carbamate categories presented in Table 3 are well known for their central nervous system toxicities.[57] Several of the specific pesticides we analyzed (2,4-D, DDT, diazinon, dicamba, and malathion) are known to be neurotoxic to the central nervous system in humans;[58] they or their metabolites must cross the blood-brain barrier. Although some of these pesticides have carcinogenic potential, in our study, exposure to pesticides with demonstrated neurotoxicity was not associated with development of glioma.

Several of the individual pesticides to which many participants were exposed (glyphosate, alachlor, metolachlor, pendimethalin, and trifluralin) have not been associated with central nervous system toxicity in humans.[59] These pesticides or their metabolites may not reach human glial cells or may not be neurotoxic. Other pesticides (atrazine and cyanazine) may cross the blood-brain barrier but are not considered neurotoxic.[59] Atrazine can cross the blood-brain barrier in rodents,[60] and it is carcinogenic in experimental animals, but tumor formation occurs by a mechanism not relevant to humans.[51] The blood-brain barrier is incompletely developed at birth, therefore, those exposed in utero or infancy might be more vulnerable to the effects of pesticides.[52,61] However, we saw no increased risk of glioma for participants born on farms where pesticides were used (results not shown).

Our population-based case-control study of gliomas is the largest to date focusing on nonmetropolitan populations. Because our controls were selected according to the distribution of gliomas by age and gender in the years preceding our study period, case-control differences in age distribution were possible and did occur: control participants were older than case participants (Table 1). The age difference is not accounted for by the ages of refusants, because the mean ages of both case and control refusants were younger than those of participants (data not shown). It is possible that cases not ascertained to the study included a higher proportion of older men than did cases that were ascertained. Our future analysis of ascertainment success when state cancer registries are used may illuminate this issue. An additional difference, although not statistically significant, was that cases were somewhat less likely to have ever lived or worked on a farm (Table 2). The statistically significant associations we saw between involvement in farm activities and exposure to pesticides (Tables 2 and 3) and reduced glioma risk might be due to a "healthy farm worker" effect[10,62] or to an association between pesticide exposure and another farm-life variable. In our study, active farmers appeared to be at lower risk of glioma. The associations were not seen when proxies were excluded, so any "healthy worker" effect would have been weak. Alternatively, underreporting of farm pesticide exposures

by proxies would have increased the proportion of those cases identified as unexposed to pesticides, and made the controls appear to be more active on farms.

The strengths of our study include the large number of histologically confirmed gliomas, the use of population-based controls, and the relatively detailed exposure assessment for a case-control study. The population-based design minimizes potential biases associated with hospital-based designs concerning the type and complexity of cases.

A weakness of our study is the high proportion (> 40%) of proxy interviews for case participants. Hospital-based rather than physician-based ascertainment might have lowered this proportion. In the hospital-based National Cancer Institute case-control glioma study, only 16% of glioma patients were interviewed by proxy,[63] whereas in the Northern California case-control glioma study, in which cases were ascertained through the cancer registry, the proportion of proxy interviews among glioma patients (46%) was similar to our study.[64]

The accuracy and completeness of information given by surrogate respondents varies by the relationship to the case, gender, race, and age of the surrogate; the specific questions asked; and how long the surrogate and the case lived together.[65–69] Brown[70] found that surrogates provided accurate information about exposures of farmers without leukemia or non-Hodgkins lymphoma to specific pesticides, but were less accurate in reporting days of use. Boyle and Braun[71] found good positive predictive value for a general variable—living or working on a farm—but lower sensitivity when proxies for cancer cases were asked about specific pesticides or durations of exposure. Johnson[65] interviewed proxies in 1990 to 1991 for case and control participants interviewed in 1981 to 1983 and found excellent agreement for general questions on whether participants had ever farmed or ever used pesticides. Agreement declined for categories of pesticide (insecticide, etc.) and was lowest (50–75%) for specific pesticides. For about one-third of pesticides, either case proxies overreported and control proxies underreported or vice versa. This misclassification affected ORs in both directions. Johnson[65] asked proxies how knowledgeable they were about the participants' pesticide use. Widows and wives (35% of the proxies) reported having less knowledge than did sons (29%), brothers (11%), sisters or daughters (10%), or other male relatives and friends (15%). According to self-reports, leukemia patients were significantly more likely than controls to have used any pesticides or animal pesticides; the odds decreased and were nonsignificant when proxy answers were used. In contrast, self-reports showed no case-control difference for 2,4-D or atrazine exposure, whereas proxy reports produced significant 2.6- and 5-fold ORs for cases in 2,4-D and atrazine exposure, respectively.[65] In a study of Parkinson's disease, Semchuk and Love[72] found much higher specificity (> 85%) than sensitivity for proxy responses on agricultural variables, including agricultural work, crop and grain farming, and herbicide, insecticide, and fungicide use. Use of proxy responses reduced the crude OR for herbicide use from 3.1 to 2.7, but it remained significant. Proxies tended to underreport agricultural exposures.[72]

Our a priori decision to conduct all analyses with and without proxy responses compensated somewhat for the high proportion of proxy responses. We considered that case participants had a disease that could affect recall during an interview, whether by differentially recalling possible exposures or by forgetting exposures, which in turn could affect the analysis. The results of the subgroup analyses with and without proxies were similar.

A major concern in case-control studies is the validity and reliability of the pesticide exposure assessment. The exposure metrics presented in this article were based on interview data and are subject to differential and nondifferential recall by the participants. We tried to minimize recall bias (tendency among cases to report exposures more accurately than controls, and to overreport, thus inflating risk estimates) by not identifying the study hypotheses to participants. Hoar[73] found that reporting of herbicide use by participants and pesticide suppliers was similar for cancer cases and controls. Inaccurate recall of pesticide identity could lead to nondifferential bias, which would bias estimates toward the null. To minimize this in reporting of individual pesticides, respondents were given detailed prompt lists of pesticides, including trade names and common names, to review visually.

Despite the accumulating number of human studies, the etiology of gliomas remains elusive. In the future, we will analyze agricultural exposures to potential carcinogens other than pesticides, as well as human exposure to pesticides in nonagricultural settings. We will also investigate whether other factors such as diet, or exposure to other chemicals including solvents and nonionizing and ionizing radiation in conjunction with farm and pesticide exposures within our study sample may shed more light on the causes of brain cancer among farmers.

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