The Upper Midwest Health Study: A Case-Control Study of Primary Intracranial Gliomas in Farm and Rural Residents

A. M. Ruder, M. A. Waters, T. Carreón, M. A. Butler, K. E. Davis-King, G. M. Calvert, P. A. Schulte, E. M. Ward, L. B. Connally, J. Lu, D. Wall, Z. Zivkovich, E. F. Heineman, J. S. Mandel, R. F. Morton, D. J. Reding, K. D. Rosenman, and the Brain Cancer Collaborative Study Group

ABSTRACT. *Since several studies indicated that farmers and agricultural workers had an excess risk of brain cancer, the National Institute for Occupational Safety and Health initiated the Upper Midwest Health Study to examine risk of intracranial glioma in the non-metropolitan population. This population-based, case-control study evaluated associations between gliomas and rural and farm exposures among adults (ages 18 to 80) in four upper midwestern states (Iowa, Michigan, Minnesota, Wisconsin). At diagnosis/selection, participants lived in non-metropolitan counties where the largest population center had fewer than 250,000 residents. Cases were diagnosed 1 January 1995 through 31 January 1997. Over 90% of 873 eligible ascertained cases and over 70% of 1670 eligible controls consented to participate. Participants and nonparticipants, evaluated for "critical questions" on main and refusant questionnaires, differed significantly in farming and occupational experience, ethnicity, education, and lifestyle. The 1175 controls were more likely than the 798 cases to have reported ever drinking alcohol (77% vs. 73%, adjusted odds ratio (OR) 0.73, 95% confidence interval (CI) 0.59-0.92) and having had panoramic dental x-rays (34% vs. 29%, OR 0.75, CI 0.61-0.92). Controls spent a greater percentage of their lives in non-metropolitan counties (78% vs. 75%, OR 0.81, CI 0.67-1.09). Among ever-farmers, controls were more likely to have had exposure to farm insecticides (57% vs. 50%, OR 0.75, CI 0.59-0.95) and farm animals (96% vs. 91%, OR 0.48, CI 0.25-0.90). Moving to a farm as an adolescent (ages 11 to 20) vs. as an adult was associated with a greater risk of glioma*

Submitted for review in March 2005 as manuscript number JASH 5822; approved for publication by the Journal of Agricultural Safety and Health of ASABE in April 2006.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

The authors are **Avima M. Ruder,** PhD, Senior Research Epidemiologist, **Martha A. Waters,** PhD, CIH, Senior Research Health Scientist, **Tania Carreón,** PhD, Fellow, **Mary Ann Butler,** PhD, Toxicologist, **Karen E. Davis-King,** MPH, Epidemiologist (former), **Geoffrey M. Calvert,** MD, MPH, Medical Officer, **Paul A. Schulte,** PhD, Division Director, **Elizabeth M. Ward,** PhD, Branch Chief (former), **L. Barbara Connally,** MS, Notification Officer, **John Lu,** MS, Programmer, **David Wall,** MAS, Statistician, and **Zach Zivkovich,** MS, MBA, Programmer, National Institute for Occupational Safety and Health, Cincinnati, Ohio; **Ellen F. Heineman,** PhD, Epidemiologist (former), National Cancer Institute, Bethesda, Maryland; **Jack S. Mandel,** PhD, MPH, Professor (former), University of Minnesota, Minneapolis, Minnesota; **Roscoe F. Morton,** MD, FACP, Mercy Medical Center, Des Moines, Iowa; **Douglas J. Reding,** MD, MPH, FACP, National Farm Medicine Center, Marshfield Clinic, Marshfield, Wisconsin; **Kenneth D. Rosenman,** MD, MPH, Michigan State University, East Lansing, Michigan; and the Brain Cancer Collaborative Study Group (see Appendix 1 for complete list of collaborators). **Corresponding author:** Avima M. Ruder, National Institute for Occupational Safety and Health, Mailstop R-16, 4676 Columbia Parkway, Cincinnati, OH 45226; phone: 513-841-4440; fax: 513-841-4486; e-mail: amr2@cdc.gov.

  ISSN 1074-7583

(OR 1.96, CI 1.13-3.39). In our study sample, farm or rural residence and summary farm exposures were associated with decreased glioma risk. However, nonparticipation by never-farming eligible controls could have affected results. Comparisons of farm chemical exposures may clarify associations between farming and glioma that others have reported.

Keywords. *Agricultural workers, Agriculture, Agrochemicals, Case-control study, Glioma, Proxy, Study design.*

Despite numerous epidemiologic studies, ionizing radiation continues to be the only established environmental cause of glioma (El-Zein et al., 2002). Although several cohort and case-control studies have investigated occupational exposures, no consistent and strong etiologic associations have been identified (El-Zein et al., 2002; Preston-Martin et al., 1989; Inskip et al., 1995).

Farmers experience a lower overall mortality than the general population. However, some studies have found that individuals (almost always men only) working on farms or in the agricultural industry had an excess risk of brain cancer ranging from 1.5 to 5.0 (Viel et al., 1998; Rodvall et al., 1996; Morrison et al., 1992; Littorin et al., 1993; Wingren and Axelson, 1992; Brownson et al., 1990; Reif et al., 1989; Musicco et al., 1988; Musicco et al., 1982), while other studies found no excess of brain cancer (Ménégoz et al., 2002; Torchio et al., 1994; Bucchi et al., 2004). Some positive studies have proposed agrochemicals, including pesticides and fertilizers, as the causative agents. Because of the excess risk, the National Institute for Occupational Safety and Health (NIOSH) initiated the Upper Midwest Health Study (UMHS) to examine risk factors for intracranial glioma in the non-metropolitan population.

Using a case-control design, this population-based study evaluated associations between gliomas and rural and farm exposures, as well as other occupational and non-occupational exposures, among rural residents in four upper midwestern states (Iowa, Michigan, Minnesota, Wisconsin). The study focused on histologically confirmed primary intracranial gliomas, International Classification of Diseases-Oncology (ICD-O) codes 938-948 (Percy et al., 1990), rather than all brain neoplasms, to reduce heterogeneity among the case population. Furthermore, brain gliomas appear to be more related to occupational risk factors than other types of brain cancer (Schlehofer et al., 1990).

Incidence, histologic type, anatomic location, and prognosis of brain cancer are age-related (Jukich et al., 2001; Ahsan et al., 1995; Salcman and Kaplan, 1991; Kornblith et al., 1987). Because the etiologies of adulthood and childhood brain cancer likely differ (Bunin, 2000; Burch et al., 1987), this study was limited in scope to adults 18 to 80 years old. When the study was initiated, then-current statistics showed that Iowa, Michigan, Minnesota, and Wisconsin were among the U.S. states with the highest brain cancer mortality rates. For 1970-1994, mean U.S. age-adjusted death rates from cancer of the brain and nervous system for white males and females were 5.2 and 3.5/ 100,000 person-years, respectively; all four study states ranked among the 15 states with the highest rates for both white males and females (Devesa et al., 1999). Rates were also high for black males and females but were based on substantially smaller numbers in these states.

This study included both men and women to determine whether risks varied by gender and whether there was evidence of a relationship between hormones or other gender-specific factors and development of intracranial brain gliomas. Few studies explicitly examined risks of brain cancer among women (Blowers et al., 1997), and the literature presents limited evidence that hormones play a role in the development of gliomas (Lambe et al., 1997; Schlehofer et al., 1990). Our study of reproductive factors

and glioma in women (Huang et al., 2004) found a relationship between the number of months a mother nursed and her risk of glioma.

Previous publications have presented our analyses of farm pesticide exposure and risk of glioma in women and men (Carreón et al., 2005; Ruder et al., 2006), which found no increased risk.

This article presents our comparison of rural and farm residence and other farm-related factors for cases and controls, and includes an overview of the study design and methods, basic comparisons of cases and controls, and characteristics of participants and nonparticipants. For these comparisons, we used responses to "critical questions," usually the first questions in full questionnaire sections (a "no" response meant the entire section was skipped) and the only questions on the refusant questionnaire.

Materials and Methods

Study Sample and Study Design

The study sample included those ages 18 to 80 residing, at diagnosis or control selection, in non-metropolitan counties of Iowa, Michigan, Minnesota, and Wisconsin and having a driver's license or state ID card (ages 18 to 64) or being on the Health Care Financing Administration's (HCFA) Medicare data tape (ages 65 to 80). We used an urban-rural continuum scale (McGranahan et al., 1986) to select non-metropolitan counties where the largest population center had fewer than 250,000 inhabitants (categories 9 to 17 in Appendix 2). Eligible counties are listed in Appendix 2. The residence criterion applied to cases at diagnosis and to controls at control selection (1 Jan. 1995). Previous or subsequent non-metropolitan-county residence did not affect eligibility. Cases or controls with a prior malignancy other than a glioma were not excluded. Cases had to have had a histologically confirmed primary intracranial glioma (ICD-O codes 938-948) diagnosed from 1 January 1995 through 31 January 1997.

Potential brain glioma case participants were identified by over 280 ascertaining physicians, 45 group practices, and 69 medical facilities in the four study states plus border-city facilities and practices in Illinois, Nebraska, North Dakota, and South Dakota. We used this rapid ascertainment system, rather than identifying cases through cancer registries, to try to complete case eligibility determination and physician consent in two to three weeks. We obtained physician consent before contacting cases or their next of kin.

Using the glioma distribution by gender and age at diagnosis (by ten-year age groups) during a three-year period (1989-1992) in the four study states, we selected potential controls (2:1 to projected number of cases), who resided in eligible counties on 1 January 1995, from state driver's license records (ages 18 to 64) or from HCFA registers (ages 65 to 80). Ethnicity was not used as a stratifying variable because the non-metropolitan counties of all four states were over 95% white non-Latino in 1990 (Bureau of Census, 2002). Sampling randomly within gender-age strata, we chose a pool of potential controls as the case enrollment period began. Controls had no diagnosis of glioma, but were not excluded with a prior diagnosis of other cancer or any other disease. We interviewed living controls (rather than their proxies to parallel the many case proxy interviews). Every attempt was made to recruit and interview both eligible cases and potential controls. The NIOSH Human Subjects Review Board (HSRB 94-DSHEFS-08) and review boards from all participating institutions approved the study, which was conducted in accordance with Subsection (m) of the Privacy Act of 1974 (5 U.S.C. 552a) and Section 308(d) of the Public Health Service Act (42 U.S.C. 242m). We will notify

participants and other respondents of overall study results according to NIOSH procedures (NIOSH, 1995).

Data Collection

The University of Minnesota study coordinating center oversaw fieldwork and reviewed pathology reports to confirm eligibility. Each state center (Mercy Foundation in Iowa, Michigan State University in Michigan, University of Minnesota in Minnesota, and Marshfield Clinic in Wisconsin) ascertained cases, located controls, contacted potential participants and proxies, conducted interviews, and obtained well water samples and biological specimens. (Authors A. M. Ruder and T. Carreón re-reviewed pathology reports for date of diagnosis, tumor site, and any mention of previous glioma. We queried the pathologists who had provided reports about ambiguities; 72 individuals who did not meet all of the case criteria were excluded from the analysis.)

After state centers mailed requests for participation in UMHS to cases and controls, or their next of kin, interviewers telephoned to arrange interview appointments. During the first telephone contact with potential case participants, interviewers asked those less than 65 years old if they had current driver's licenses and those over 65 if they were enrolled in Medicare, to determine final eligibility. Before the in-person interview, the interviewer administered informed consent. State centers mailed consent forms and prepaid return envelopes to those interviewed by telephone.

For women, the preferred proxy was a first-degree female relative who would know the subject's reproductive history. For men, the preferred proxy was a relative knowledgeable about farming and occupational histories (sometimes a wife, but usually a brother or son). In some cases, different family members were proxies for different sections of the questionnaire (e.g., brother for farm history, wife for residential history).

We asked eligible individuals declining participation to complete a brief refusant interview by telephone.

For those participating, we used a questionnaire, modified for use in the present study, based on one that NCI developed for a telephone interview study (Chen et al., 2002). Interviewers recorded information on demographics, medical history, potential confounders, exposures of interest, and complete residential and occupational histories.

The interviewer and state coordinator each reviewed the completed questionnaires. After data entry, a third review focused on discrepancies among the "critical questions" (which corresponded to questions on the refusant questionnaire). A "critical question" was usually the first question in a full questionnaire section; a "no" response meant the entire section was skipped. Followbacks generated by this review were sent to the state centers for resolution, with repeat phone calls to respondents where necessary and possible.

Due to the nature of the study, it was not possible to blind the interviewers completely to case/control status. To minimize interviewer bias, we conducted intensive interviewer training, used a standardized interview, interviewed cases and controls in the same manner, and kept the interviewers blind to the study hypotheses (Schlesselman et al., 1982). The coordinating center trained interviewers from all four states in joint sessions, stressing the importance of an unbiased interview, placing emphasis on both verbal and non-verbal means of bias. After every tenth interview by an interviewer, the state coordinator conducted a brief telephone re-interview of the respondent, focusing on critical questions. The coordinator compared interviewer verification and full questionnaires and re-trained interviewers as necessary to reduce the occurrence of discrepancies.

On each section of the questionnaire, the interviewer noted, after completing that section, the respondent's relation to the participant. Respondent tallies were reviewed, blinded to case-control status. If the total contribution of the participant was less than

75% (i.e., other respondents had provided more than 25%), then the "participant only" interview was reclassified as "participant + proxy". If the total contribution of the participant was less than 5%, then the "participant + proxy" interview was reclassified as "proxy only". In addition, for about 10% of cases, a proxy respondent completed an interview (about a case previously interviewed in person and later deceased) to determine the limits of proxy recall of case life histories (not explored here).

Exposure Assessment

Interviewers asked all case participants interviewed in person (rather than by proxy) and approximately 70% of control participants (pre-selected) to donate a blood specimen. Trained phlebotomists (interviewers or other staff) collected specimens at the time of the interview or later. We also asked case participants or their proxy respondents to release a brain tissue specimen if one had been collected during previous surgery or biopsy. DNA extracted from lymphocytes and tissue is being genotyped for susceptibility markers. Interviewers asked participants who had used the same private well for drinking water from 1983 to 1993 to provide a water sample (collected by the interviewer) to be tested for nitrate-nitrite content.

Rather than collect exposure data through the date of the interview (or death, for deceased participants), we set a cutoff date for all histories and other exposure information, because more recent exposures would not be relevant to etiology (Rothman, 1981). The date chosen (1 Jan. 1993) was near the beginning of a new presidential term, a life event that all respondents would likely remember (Engel et al., 2001). Interviewers mentioned this event at the beginning of the interview. (Copies of the questionnaire are available on request from the first author.)

Statistical Analyses

We hypothesized that farm and non-metropolitan residence increase the risk for intracranial brain gliomas. In-depth analyses adjusted all estimates of association through modeling. Multiple logistic regression models controlling for gender and age group (the stratifying variables), age, and education (as a partial surrogate for socioeconomic status) in case-control comparisons were run to obtain maximum-likelihood estimates of the adjusted odds ratio (OR) and 95% confidence interval (CI) (Breslow and Day, 1980). All analyses used SAS 8.0 software (SAS, 1999).

The metric used to control for age was "age on 1 January 1993" (the cutoff date used in the questionnaire). "Age at interview" was not used because many cases had died before the interview and because, on the average, controls were interviewed earlier than cases. "Age at case diagnosis" was not used because controls were frequency matched rather than individually matched to cases.

Because of the expected high percentage of proxy interviews, we decided *a priori* not to make a statistical adjustment for the type of respondent. Instead, for all in-depth analyses, we performed separate analyses and calculated odds ratios using data only from participants, and from participants and proxies combined (Walker et al., 1988).

Results

The total potential study sample included 2876 individuals. There were 1789 potential control participants (1008 men and 781 women) and 1087 ascertained putative cases (611 men and 476 women). Control and case review eliminated 215 ineligible cases (117 men and 98 women) and 120 ineligible controls (75 men and 45 women). The final study pool included 872 eligible cases (494 men and 378 women) and 1669 eligible controls (933 men and 736 women), among whom 798 cases (92%) and 1175 controls

(70%) participated in the study. Proxies for 360 cases and 34 controls were interviewed, with two or more proxies participating in, respectively, 35% and 15% of interviews. In addition, 137 case and 49 control interviews included a proxy as well as the study participant, with two or more proxies assisting in 16% and 4% of these interviews, respectively. Most participants were interviewed in person, but there were 155 telephone interviews (state centers mailed consent forms to 76 controls, 7 control proxies, 24 cases, and 48 case proxies interviewed by telephone).

Table 1 presents reasons for ineligibility and numbers excluded as well as reasons for nonparticipation. Case ascertainment, assessed by comparison with respective state tumor registry ascertainment for eligible counties, was 78% overall and, by state, 86% in Iowa, 86% in Michigan, 84% in Minnesota, and 62% in Wisconsin. Our Wisconsin collaborators had some difficulty in ascertaining cases in the southernmost Wisconsin counties. However, this difficulty was not associated with case age, gender, or histology. We ran several analyses excluding Wisconsin participants to see if the results were

Table 1. Reasons for ineligibility and non-participation of potential participants.

	Males				Females			
	Potential Cases		Potential Controls		Potential Cases		Potential Controls	
Characteristics	*n*	%	*n*	%	*n*	%	*n*	%
Possible participants	611	100	1008	100	476	100	781	100
Case or control								
Ineligible residence	14	2.3	38	3.8	15	3.2	19	2.4
No driver's license, age 18-64	2	0.3	4	0.4	3	0.6	3	0.4
Other reasons for ineligibility[a]	3	0.5	6	0.6	4	0.8	6	0.6
Case only								
Ineligible age	4	0.7	--		11	2.3	--	
Ineligible histology or site	16	2.6	--		19	4.0	--	
Ineligible date of diagnosis	36	5.9	--		13	2.7	--	
Insuff. data to verify eligibility	24	3.9	--		16	3.3	--	
Duplicate ascertainment	18	2.9	--		17	3.6	--	
Control only								
Deceased before eligibility date	--		11	1.1	--		2	0.3
Ineligible by control selection	--		16	1.6	--		15	1.9
Eligible potential participants	494	81	933	93	378	79	736	94
Nonparticipation	37	7.4[c]	285	30.5[c]	37	9.8[c]	209	28.4[c]
MD refusal	10	2.0[c]	--		10	2.6[c]	--	
Potential participant refusal	4	0.8[c]	183	19.6[c]	5	1.3[c]	154	20.9[c]
Next-of-kin refusal	14	2.8[c]	12	1.3[c]	13	3.4[c]	4	0.5[c]
Potential participant or next-of-kin unavailable[b]	9	1.8[c]	90	9.6[c]	9	2.4[c]	51	6.9[c]
Eligible contacted nonparticipants completing refusant interview	9/18	50[d]	60/195	31[d]	4/18	22[d]	70/158	44[d]
Study participants[e]	457	92.5[c]	648	69.5[c]	341	90.7[c]	527	71.6[c]

[a] Other reasons include: no suitable proxy found, wrong person interviewed, etc.
[b] Unlocatable, deceased, ill, or non-English speaking.
[c] Percentage among eligible potential participants.
[d] Percentage among eligible potential participants (or proxies) we were able to contact.
[e] Totals include 73 controls (39 men, 34 women) and 20 cases (13 men, 7 women) originally completing a refusant interview and later becoming full participants.

significantly affected; they were not. To confirm that controls were distributed at random geographically, we compared the distribution of controls by county with the population distribution by county, within the eligible counties, using the most recent Census data. The correlation was 0.85 ($p < 0.0001$).

All eligible participants and nonparticipants are compared for demographic characteristics (age and state of residence) in table 2. Participating cases (mean age 51.8 ±16.1) are younger than participating controls (mean age 54.6 ±15.4) and non-participating cases (mean age 53.7 ±14.3). Non-participating controls are the oldest group (mean age 57.5 ±15.1). Table 2 also presents the diagnoses for participating and nonparticipating cases. The distributions by histology are similar for participants and nonparticipants.

Table 3 compares participants with the 37% of nonparticipants (142/389 contacted potential participants) who completed only a brief telephone refusant interview (the questions in the table and a few others). Ever having lived on a farm, having raised animals on a farm, having watched more TV, having had a non-farm job, ever having handled pesticides on a non-farm job, being of white non-Latino ethnicity, having completed high school, and, for women, and ever having been pregnant were positively associated with participation. Participants who had completed a refusant interview and later agreed to full participation were compared to both always-refusants and always-participants. Former refusants were more likely than other participants to live in Iowa or Wisconsin and to have less than a high school education. Former refusants were

Table 2. Characteristics of eligible participants and non-participants.[a]

	Participants				Nonparticipants			
	Cases (798)		Controls (1175)		Cases (74)		Controls (494)	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Age (years)[b]								
18-30	103	13	115	10	5	7	74	15
31-40	120	15	128	11	12	16	66	13
41-50	123	15	157	13	7	9	70	14
51-60	159	20	252	21	18	24	83	17
61-70	192	24	359	31	18	24	136	24
71-80	101	13	164	14	14	19	65	13
State of residence								
Iowa	190	24	302	26	18	24	85	17
Michigan	246	31	298	25	29	39	144	29
Minnesota	163	20	257	22	18	24	83	17
Wisconsin	199	25	318	27	9	12	182	37
Histology (ICD-O codes)[c]								
Glioma (93803-93923)	56	7			7	9		
Astrocytoma (94003-94243)	172	22			9	12		
Glioblastoma (94403-94433)	472	59			52	70		
Oligodendroglioma (94503-94513)	86	11			5	7		
Medulloblastoma/PNET (94703-94733)	12	1			1	1		

[a] Age, state of residence information, and gender were available for all potential eligible participants, and histology was available for potential eligible cases.

[b] Age on 1 January 1993. Eligibility required age ≥18 at diagnosis (1 Jan. 1995 to 31 Jan. 1997) or control selection (1 Jan. 1995).

[c] χ^2 for histology distribution = 5.89; four degrees of freedom; $p > 0.10$.

Table 3. Characteristics of eligible participants and non-participants who completed refusant interview.

	Participants				Interviewed Nonparticipants[a]			
	Cases (798)		Controls (1175)		Cases (13)		Controls (130)	
Characteristic	*n*	%	*n*	%	*n*	%	*n*	%
Ever lived/worked on farm	478	60	753	64	6	46	56	43[b]
Total years on farm								
≤20	293	37	407	35	1	8	31	24
21-40	86	11	171	15	0	0	4	3
>40	91	11	172	15	2	15	15	11
Pesticides ever used	268/478	56	480/753	64	0/6	0	32/56	57
Lived on farm after age 18	268/478	56	463/753	62	--		--	
Raised cattle, hogs, or chickens[c]	241/268	91	443/463	96	2/6	33	53/56	95
Used solvent to clean on farm[c]	86/268	32	167/463	36	2/6	33	30/56	54[b]
Non-farming job ≥1 year	762	96	1105	94	13	100	104	81[b]
Pesticides on non-farm job	70/762	9	119/1105	11	0/13	0	3/104	3[b]
Longest job								
Professional	234	31	345	31	2	15	27	26
Trades	296	39	412	37	8	62	41	39
Service	230	30	346	31	3	23	36	35
TV hours/day after age 18[d]								
1-3	546/751	73	863/1128	76	8/9	89	83/118	70[b]
>4	191/751	25	257/1128	23	1/9	11	33/118	28
Hay fever/allergy prescription	88	11	143	12	2	15	12	9
Ever panoramic dental x-ray	230	29	394	34	2	15	36	28
White non-Latino	783	98	1152	98	13	100	116	89[b]
Education								
<12 years	144	18	207	18	4	31	40	31[b]
High school graduate	522	65	767	65	8	62	70	54
College graduate	132	17	201	17	1	8	20	15
Women								
Ever pregnant	300/341	88	458/527	87	2/4	50	50/70	71[b]
Number of pregnancies								
1-3	182	53	239	45	2	50	26	37
4-6	94	28	172	33	0	0	19	27
>7	24	7	47	9	0	0	5	7
Menstruating through 1992	130	38	159	30	2	50	14	20

[a] Nonparticipants completing brief refusant telephone interview (9 male cases, 60 male controls, 4 female cases, 70 female controls). Refusants who later became participants are not included among refusants in these comparisons. Questions on the refusant questionnaire were "critical" because in a full questionnaire section they were usually the first question; "no" respondents skipped the entire section. Question format differed on full and refusant questionnaires.

[b] Participating and nonparticipating controls' responses differed significantly ($p < 0.05$).

[c] Asked of all refusants but only of participants living or working on a farm after age 18.

[d] Asked of all refusants but only of participants 18 or older by 1992.

more likely than refusants to be white non-Latinos, to be Iowa residents, to have had a job and lived on a farm, and, if women, to be younger and to have ever been pregnant.

Adjusted ORs for the risk of glioma for "critical questions" and other key demographic factors (smoking, drinking alcohol), including and excluding proxy

Table 4. Characteristics of cases and controls and risk of glioma, according to respondent status.

	Including Proxy-Only Interviews[a]			Excluding Proxy-Only Interviews[a]		
	Cases (798)	Controls (1175)	OR (95% CI)[b]	Cases (438)	Controls (1141)	OR (95% CI)[b]
Ever non-farm job ≥1 year (vs. never)	762	1105	1.36 (0.89-2.08)	414	1076	1.05 (0.63-1.76)
Ever pesticides on non-farm job (vs. never)	70/ 762	119/ 1105	0.77 (0.56-1.06)	36/ 414	118/ 1076	0.64 (0.43-0.96)
Longest job						
Professional	234	345	Referent	141	337	Referent
Trades	296	412	0.97 (0.74-1.27)	146	398	0.86 (0.61-1.20)
Service	230	346	0.94 (0.72-1.23)	125	339	0.82 (0.59-1.13)
TV hours/day after age 18[c, d]	2.7 ±1.7	2.6 ±1.4	1.05 (0.98-1.11)	2.7 ±1.6	2.6 ±1.4	1.01 (0.94-1.10)
Hay fever/allergy prescription (vs. none)	88	143	0.82 (0.62-1.10)	54	139	0.78 (0.55-1.11)
Ever panoramic dental x-ray (vs. never)	230	394	0.75 (0.61-0.92)	134	388	0.67 (0.52-0.86)
White non-Latino (vs. all other)	783	1152	1.36 (0.70-2.66)	429	1119	1.43 (0.64-3.20)
Education						
College graduate	132	201	Referent	89	199	Referent
High school graduate	522	767	1.11 (0.87-1.43)	303	751	1.0 (0.7-1.3)
<12 years	144	207	1.31 (0.95-1.82)	46	191	1.0 (0.6-1.5)
Smoking						
Never	363	526	Referent	222	514	Referent
Former	236	422	0.89 (0.71-1.11)	99	407	0.68 (0.51-0.91)
Current (through 1 Jan. 1993)	199	227	1.21 (0.94-1.55)	117	220	1.02 (0.76-1.38)
Ever drank alcohol (vs. never)	582	900	0.73 (0.59-0.92)	328	881	0.73 (0.55-0.98)
Women						
Ever pregnant (vs. never)	300/ 341	458/ 527	1.20 (0.75-1.93)	169/ 196	449/ 516	1.31 (0.72-2.39)
Number of pregnancies[d]	3.5 ±2.0	3.9 ±2.3	0.96 (0.89-1.03)	3.4 ±1.8	3.9 ±2.3	1.00 (0.91-1.11)
Menstruating through 1992 (vs. postmenopausal)	130	159	0.64 (0.37-1.10)	112	159	1.13 (0.59-2.19)

[a] Includes subject + proxy interviews for 137 cases and 49 controls.
[b] Adjusted for age, ten-year age strata, education, state, and gender (except for women-only variables).
[c] Continuous variable (mean, SD); OR is for one unit (year, hour, pregnancy).
[d] Question asked only of participants 18 or older by 1992.

Table 5. Farm-related factors and risk of glioma, according to respondent status.

Characteristic	Including Proxy-Only Interviews[a] Cases (798)	Controls (1175)	OR (95% CI)[b]	Excluding Proxy-Only Interviews[a] Cases (438)	Controls (1141)	OR (95% CI)[b]
Percent of life in non-metropolitan counties[c]	75.1 ±33.5	78.2 ±32.3	0.81 (0.61-1.09)	75.0 ±34.8	78.0 ±32.4	0.83 (0.58-1.19)
Percent of life on farms[c]	22.8 ±31.7	25.9 ±32.7	0.81 (0.60-1.09)	21.9 ±32.0	25.8 ±32.7	0.94 (0.64-1.38)
Ever lived/worked on farm	478	753	0.89 (0.74-1.09)	245	729	0.91 (0.72-1.17)
Total years on farm[c]	23.1 ±19.9	25.2 ±20.8	1.00 (0.99-1.01)	21.2 ±18.3	25.0 ±20.6	1.00 (0.99-1.01)
Age first on farm	12.3 ± 20.2	11.2 ±19.9		11.9 ±18.5	11.3 ±19.9	
Infant (<1 year)	283	474	1.06 (0.79-1.43)	140	455	1.19 (0.81-1.76)
Child (1-10)	47	74	1.03 (0.66-1.61)	24	74	1.06 (0.59-1.89)
Adolescent (11-20)	37	30	1.96 (1.13-3.39)	22	30	2.21 (1.13-4.34)
Adult (21+)	111	175	Referent	59	170	Referent
Farm acreage (if known/ estimated)	279 ±653 (n = 377)	251 ±541 (n = 645)	1.00 (1.00-1.00)	325 ±674 (n = 207)	252 ±547 (n = 631)	1.00 (1.00-1.00)
Pesticides ever used	268	480	0.72 (0.57-0.92)	153	470	0.91 (0.66-1.25)
Insecticides	237	429	0.75 (0.59-0.95)	136	422	0.96 (0.71-1.31)
Herbicides	192	317	0.89 (0.70-1.13)	115	311	1.02 (0.75-1.40)
Fungicides	37	63	0.89 (0.58-1.36)	22	63	0.95 (0.56-1.63)
Lived on farm after age 18	268	463		136	450	
Ever raised milk cows, other cattle, hogs, or chickens[d]	241/268	443/463	0.48 (0.25-0.90)	123/136	432/450	0.56 (0.25-1.25)
Ever used gasoline, mineral spirits, or other solvent to clean on farm[d]	86/268	167/463	0.75 (0.55-1.02)	55/136	165/450	0.99 (0.67-1.44)

[a] Includes 137 case and 49 control subject + proxy interviews.
[b] Adjusted for age, ten-year age groups, education, gender, and state.
[c] Continuous variable (mean, SD); OR is for one unit (year, percentage point).
[d] Question asked only of participants who lived or worked on a farm after age 18.

responses, are presented in table 4. In analyses including proxy responses, controls were significantly more likely than cases to have reported having had a panoramic dental x-ray. Current (as of 1 Jan. 1993) smoking was associated with increased risk of glioma, while ever drinking alcohol had the opposite association. For almost all the variables in table 4, the ORs for analyses excluding proxies were in the same direction, although the confidence intervals were broader because the sample size was smaller. However, for "menstruation through [the end of] 1992", the ORs were reversed: including proxies, the

ORs associated with still menstruating was 0.64; excluding proxies, the OR was 1.13 (neither statistically significant).

Table 5 shows the risk of glioma, including and excluding proxy responses, for responses on farm-related factors. We analyzed residential histories for location of each residence in a metropolitan or non-metropolitan county and categorization of each residence as a farm or non-farm. Controls spent a greater percentage of their lives residing in non-metropolitan counties and on farms. Our study design required that controls be living in an eligible county at control selection (1 Jan. 1995) and cases at their date of diagnosis (1 Jan. 1995 to 31 Jan. 1997). Because the residential history ended at 1 January 1993, we did not have information for everyone on residence on 1 January 1995. We did, however, conduct a sensitivity analysis, excluding the 54 controls and 63 cases who were not residing in an eligible county on 1 January 1993. Results (not shown) were similar to those including all eligible participants. In analyses including proxy responses, among those who lived on a farm, controls were significantly more likely than cases to have reported exposure to farm insecticides. Among those who lived on a farm as adults, controls were significantly more likely than cases to have reported exposure to farm animals and to having used gasoline or other solvents to clean up on the farm. ORs for analyses excluding proxies were in the same direction. Those who first lived on a farm in their teens (vs. as an adult) had a significantly increased risk of glioma: OR 1.96 (1.13-3.39) including proxy interviews; OR 2.21 (1.13-4.34) excluding proxy interviews.

Discussion

Our case-control study of gliomas is the largest to date focusing on non-metropolitan populations. The strengths of our study included the large number of histologically confirmed gliomas and the use of population-based controls, and the successful collection of biological specimens from a majority of participants.

Among the cases, there were no significant differences in participation by diagnosis (table 2), although nonparticipants were more likely to have had a diagnosis of glioblastoma. Such differences could affect results if different histologies represent different etiologies. We think this difference represents the combined effects of the poorer survival of glioblastoma patients and the greater refusal rate of proxies (vs. patients themselves).

Since our pool of potential controls was drawn from non-urban counties, we expected a high proportion of farmers. Of participating controls, 64% had ever lived or work on a farm. Participants and nonparticipants differed significantly in farming and occupational experience, ethnicity, education, and lifestyle (table 3). Previous studies have shown that those declining to participate in studies may differ from participants by ethnicity, socioeconomic status, and lifestyle factors (Muth et al., 2000; Walker et al., 1987; Criqui et al., 1978). Note that the 37% of nonparticipants who agreed to the refusant interview may not be a representative sample of all nonparticipants. However, if the proportion of all nonparticipating controls who were farmers was similar to that on the refusant questionnaire (43%) rather than that among participating controls (64%), then our ORs for farm-related factors could have been biased downward.

Controls were more likely than cases to report having had panoramic x-rays (table 4). Since radiation is a known cause of brain cancer, this finding could be due to better recall of medical procedures by controls than by cases with memory problems (Weitzner, 1999) or by proxies (Robbins et al., 2000). A study comparing recall with dental records found substantial disagreement for both cases and controls (Berrington de Gonzalez et al.,

2003); we did not request medical and dental records and therefore cannot make this comparison. An Australian case-control study found no excess risk of glioma among participants reporting panoramic x-rays, while this study and another in California found increased risk for meningioma among those reporting panoramic x-rays (Ryan et al., 1992; Preston-Martin et al., 1985; Rajmil et al., 1999).

Controls spent a greater percentage of their lives in non-metropolitan counties and on farms than did cases (table 5). The percentages of life on farms and in non-metropolitan counties are similar for analyses with and without proxy respondents. This finding was unexpected, given the established excess of brain cancer among farmers. However, the criterion of non-metropolitan residence at diagnosis or selection did not rule out urban residence before or after that point in time. Our study design required that controls be living in an eligible county by control selection (1 Jan. 1995) and cases by their dates of diagnosis (1 Jan. 1995 to 31 Jan. 1997). To explore whether this difference could bias the results, we conducted a sensitivity analysis, excluding the 54 controls and 63 cases who were not residing in an eligible county on 1 January 1993 (because the residential history ended at 1 Jan. 1993, we did not have information for everyone on residence on 1 Jan. 1995). Results (not shown) were similar to those including all eligible participants. It is possible that both cases with memory problems and case proxies misclassified past residences as non-farms.

Controls reported more farm pesticide exposure than did cases. However, the percentage of cases reporting exposure was higher when proxies were excluded. This could indicate that some proxies were unaware of the extent of case farm experience. Alternatively, cases could have overreported their exposure to pesticides. Whether the analyses included or excluded proxies, a greater percentage of controls than of cases reported exposure to farm pesticides. Pesticide exposure might be associated with a factor we did not ask about, such as the physical strength to do farm work. Some authors have proposed a "healthy farm worker" effect to account for the lower mortality of farmers (Torchio et al., 1994; Thelin and Hoglund, 1994). Such an effect might also explain the greater percentage of controls reporting exposure to farm animals and to gasoline or other solvents used for cleanup.

We found an increased risk of glioma associated with first living on a farm during adolescence (table 5). Recent reviews on vulnerability to environmental exposures by age have documented greater vulnerability at lower ages, although for most toxicants, younger children are at higher risk than adolescents (Brent et al., 2004; Brent and Weitzman, 2004). The increased risk we observed may have occurred by chance.

The results of our study indicate no increased risk of glioma associated with farm residence, use of broad categories of pesticides, and other farm-related characteristics, but an increased risk associated with first living on a farm during adolescence. Our findings are consistent with those of another population-based case-control study among farm residents (Ménégoz et al., 2002). A recent meta-analysis of brain cancer and farming found a 1.3 relative risk overall (Khuder et al., 1998). However, some studies had negative findings, many did not control for histological type, and many were quite small (i.e., fewer than 50 cases) (Khuder et al., 1998).

The major weakness of our study was the high (>40%) proportion of proxy interviews for case participants. Hospital-based rather than physician-based ascertainment might have lowered this proportion. In the hospital-based NCI case-control glioma study, only 16% of glioma patients were interviewed by proxy (Inskip et al., 2001), while the northern California case-control glioma study, ascertaining cases through the cancer registry, had a proxy-interview rate for cases (46%) similar to ours (Wrensch et al., 1997). For most variables, analyses including or excluding proxies had similar results. However, in analyses including proxy responses, 38% of female cases (mean age 52) were still

menstruating; excluding proxy responses, 57% of female cases (mean age 45) were still menstruating (table 4). Clearly, this shift occurred because older case women had poorer survival and were more likely to have had proxy respondents.

Because we used the distribution of gliomas by age and gender in the years preceding our study period to select controls, case-control differences in age distribution were possible. We corrected for this difference in all analyses by adjusting for age and age group stratum.

Recall bias for occupational exposures could not be assessed by comparing respondent answers to data from independent sources because thousands of workplaces were involved. In the absence of a "gold standard," methods to assess the likely impact of recall bias include using patients with other diseases as controls (Schlesselman et al., 1982). We did not consider this method for minimizing recall bias appropriate for our study, due to differences in hospital referral patterns and the fact that gliomas, other cancers, and neurological diseases may share risk factors. Questions about exposures etiologically unrelated to the disease, but that might be perceived as associated with the disease, can test for recall bias: if a strong association is found, the possibility of recall bias cannot be excluded. The length of our questionnaire precluded use of this method. However, some questionnaire sections inherently provide insight into the possibility of recall bias. For example, if cases reported uses of categories of pesticides more thoroughly, one would expect to find elevated odds ratios for insecticides, herbicides, and fungicides. However, this did not occur in our study.

Another source of bias arises from the use of proxy respondents. We estimated that 15% to 30% of all cases would be cognitively impaired or deceased and therefore not able to be interviewed. The accuracy and completeness of information given by proxy respondents varies by the proxy's relationship to the case; the gender, race, and age of the proxy, the specific questions asked; the level of detail expected in the response; and how long the proxy and the case lived together (Grigoletto et al., 1994; Johnson et al., 1993; Brown et al., 1991; McLaughlin et al., 1987; Humble et al., 1984; Pickle et al., 1983; Kolonel et al., 1977). Researchers have found proxy respondents accurate in reporting general exposure information on occupational histories, with accuracy declining as specificity increases (Fryzek et al., 2000; Hansen et al., 1997; Semchuk and Love, 1995).

Due to the nature of this study, case participant interviews were with individuals whose disease could affect recall, whether by differentially recalling possible exposures or by forgetting exposures (Weitzner, 1999), and a sizable proportion of case interviews were with proxies. Since case participant responses were not a true "gold standard" (such as a medical or occupational record) and since the direction of bias by proxies is not predictable, we did not correct proxy responses toward participant responses (Wacholder et al., 1993; Brenner, 1996; Halabi et al., 1992; Nevitt et al., 1992; Bond et al., 1988; Rosenberg et al., 1987). Instead, our *a priori* decision to conduct all in-depth analyses with and without proxy responses compensated for the high proportion of proxy responses. The consistency of our results, with and without proxy responses, validates the use of proxy respondents.

In our study sample, farm or rural residence and farm exposures were associated with decreased glioma risk, although first living on a farm as an adolescent was associated with increased glioma risk. However, it is possible that nonparticipation by never-farming eligible controls could have affected results, since we do not know how many of the 364 refusant controls who did not do a refusant interview ever farmed. Comparison of farm chemical exposures and farm activities may clarify the association between farming and glioma that others have reported, as well as some of the current ambiguities in the etiology of this disease.

Acknowledgements

We thank study participants, physicians, participating institutions and staff, NIOSH staff who assisted, and intramural and extramural reviewers for helpful comments. This study was funded in part by the NIOSH Initiative for Cancer Control Projects for Farmers and in part by CDC/NIOSH operating funds. The NIOSH Human Subjects Review Board (HSRB 94-DSHEFS-08) and review boards from all participating institutions approved the study, which was conducted in accordance with Subsection (m) of the Privacy Act of 1974 (5 U.S.C. 552a) and Section 308(d) of the Public Health Service Act (42 U.S.C. 242m).

References

Ahsan, H., A. I. Neugut, and J. N. Bruce. 1995. Trends in incidence of primary malignant brain tumors in USA, 1981-1990. *Intl. J. Epidemiol.* 24(6): 1078-1085.

Berrington de Gonzalez, A., A. Ekbom, A. G. Glass, M. R. Galanti, L. Grimelius, M. J. Allison, and P. D. Inskip. 2003. Comparison of documented and recalled histories of exposure to diagnostic x-rays in case-control studies of thyroid cancer. *American J. Epidemiol.* 157(7): 652-663.

Blowers, L., S. Preston-Martin, and W. J. Mack. 1997. Dietary and other lifestyle factors of women with brain gliomas in Los Angeles County (California, USA). *Cancer Causes Control* 8(1): 5-12.

Bond, G. G., K. M. Bodner, W. Sobel, R. J. Shellenberger, and G. H. Flores. 1988. Validation of work histories obtained from interviews. *American J. Epidemiol.* 128(2): 343-351.

Brenner, H. 1996. Correcting for exposure misclassification using an alloyed gold standard. *Epidemiology* 7(4): 406-410.

Brent, R. L., S. Tanski, and M. Weitzman. 2004. A pediatric perspective on the unique vulnerability and resilience of the embryo and the child to environmental toxicants: The importance of rigorous research concerning age and agent. *Pediatrics* 113(4 supp.): 935-944.

Brent, R. L., and M. Weitzman. 2004. The current state of knowledge about the effects, risks, and science of children's environmental exposures. *Pediatrics* 113(4 supp.): 1158-1166.

Breslow, N. E., and N. E. Day. 1980. *Statistical Methods in Cancer Research: The Analysis of Case-Control Studies.* 1st ed. Lyon, France: International Agency for Research on Cancer, World Health Organization.

Brown, L. M., M. Dosemeci, A. Blair, and L. Burmeister. 1991. Comparability of data obtained from farmers and surrogate respondents on use of agricultural pesticides. *American J. Epidemiol.* 134(4): 348-355.

Brownson, R. C., J. S. Reif, J. C. Chang, and J. R. Davis. 1990. An analysis of occupational risks for brain cancer. *American J. Public Health* 80(2): 169-172.

Bucchi, L., O. Nanni, A. Ravaioli, F. Falcini, R. Ricci, E. Buiatti, and D. Amadori. 2004. Cancer mortality in a cohort of male agricultural workers from northern Italy. *J. Occup. Environ. Med.* 46(3): 249-256.

Bunin, G. 2000. What causes childhood brain tumors? Limited knowledge, many clues. *Pediatr. Neurosurg.* 32(6): 321-326.

Burch, J. D., K. J. Craib, B. C. Choi, A. B. Miller, H. A. Risch, and G. R. Howe. 1987. An exploratory case-control study of brain tumors in adults. *J. Nat. Cancer Inst.* 78(4): 601-609.

Bureau of the Census. 2002. State and County QuickFacts. Washington, D.C.: U. S. Commerce Department. http://quickfacts.census.gov/qfd/.

Carreón, T., M. A. Butler, A. M. Ruder, M. A. Waters, K. E. Davis-King, G. M. Calvert, P. A. Schulte, L. B. Connally, W. Sanderson, E. M. Ward, E. F. Heineman, J. S. Mandel, R. F. Morton, D. J. Reding, K. D. Rosenman, G. Talaska, and the Brain Cancer Collaborative Study Group. 2005. Gliomas and farm pesticide exposure in women: The Upper Midwest Health Study. *Environ. Health Perspect.* 113(5): 546-551.

Chen, H., M. H. Ward, K. L. Tucker, B. I. Graubard, R. D. McComb, N. A. Potischman, D. D. Weisenburger, and E. F. Heineman. 2002. Diet and risk of adult glioma in eastern Nebraska, United States. *Cancer Causes Control* 13(7): 647-655.

Criqui, M. H., E. Barrett-Connor, and M. Austin. 1978. Differences between respondents and non-respondents in a population-based cardiovascular disease study. *American J. Epidemiol.* 108(5): 367-372.

Devesa, S. S., D. G. Grauman, W. J. Blot, G. Pennello, R. N. Hoover, J. F. Fraumeni, Jr. 1999. *Atlas of Cancer Mortality in the United States, 1950-94.* Washington, D.C.: U.S. Government Printing Office.

El-Zein, R., A. Y. Minn, M. Wrensch, M. L. Bondy. 2002. Epidemiology of brain tumors. In *Cancer in the Nervous System*, 252-266. V. A. Levin, ed. New York, N.Y.: Oxford University Press.

Engel, L. S., M. C. Keifer, M. L. Thompson, and S. H. Zahm. 2001. Test-retest reliability of an icon/calendar-based questionnaire used to assess occupational history. *American J. Ind. Med.* 40(5): 512-522.

Fryzek, J. P., L. L. Lipworth, D. H. Garabrant, and J. K. McLaughlin. 2000. Comparison of surrogate with self-respondents for occupational factors. *J. Occup. Environ. Med.* 42(4): 424-429.

Grigoletto, F., D. W. Anderson, W. A. Rocca, F. Meneghini, L. Morgante, A. Reggio, G. Savettieri, and R. Di Perri. 1994. Attrition and use of proxy respondents and auxiliary information in the Sicilian Neuroepidemiologic Study. *American J. Epidemiol.* 139(2): 219-228.

Halabi, S., H. Zurayk, R. Awaida, M. Darwish, and B. Saab. 1992. Reliability and validity of self and proxy reporting of morbidity data: A case study from Beirut, Lebanon. *Intl. J. Epidemiol.* 21(3): 607-612.

Hansen, J., P. Boffetta, A. Andersen, J. W. Cherrie, J. Chang-Claude, U. Eilber, R. Frentzel-Beyme, T. Hemmingsson, J. H. Olsen, N. Plato, R. Saracci, G. B. Skare, and P. Westerholm. 1997. Comparison of information on occupation and lifestyle habits obtained from European man-made vitreous fibre production workers and their relatives. *Intl. J. Epidemiol.* 26(5): 1009-1016.

Huang, K., E. A. Whelan, A. M. Ruder, E. M. Ward, J. A. Deddens, K. E. Davis-King, T. Carreon, M. A. Waters, M. A., Butler, G. M. Calvert, P. A. Schulte, Z. Zivkovich, E. F. Heineman, J. S. Mandel, R. F. Morton, D. J. Reding, and K. D. Rosenman. 2004. Reproductive factors and risk of glioma in women. *Cancer Epidemiol. Biomarkers Prev.* 13(10): 1583-1588.

Humble, C. G., J. M. Samet, and B. E. Skipper. 1984. Comparison of self- and surrogate-reported dietary information. *American J. Epidemiol.* 119(1): 86-98.

Inskip, P. D., M. S. Linet, and E. F. Heineman. 1995. Etiology of brain tumors in adults. *Epidemiol. Rev.* 17(2): 382-414.

Inskip, P. D., R. E. Tarone, E. E. Hatch, T. C. Wilcosky, W. R. Shapiro, R. G. Selker, H. A. Fine, P. M. Black, J. S. Loeffler, and M. S. Linet. 2001. Cellular telephone use and brain tumors. *New England J. Med.* 344(2): 79-86.

Johnson, R. A., J. S. Mandel, R. W. Gibson, J. H. Mandel, A. P. Bender, P. D. Gunderson, and C. M. Renier. 1993. Data on prior pesticide use collected from self- and proxy respondents. *Epidemiology* 4(2): 157-164.

Jukich, P. J., B. J. McCarthy, T. S. Surawicz, S., Freels, and F. G. Davis. 2001. Trends in incidence of primary brain tumors in the United States, 1985-1994. *Neuro-Oncol.* 3(3): 141-151.

Khuder, S. A., A. B. Mutgi, and E. A. Schaub. 1998. Meta-analyses of brain cancer and farming. *American J. Ind. Med.* 34(3): 252-260.

Kolonel, L. N., T. Hirohata, and A. M. Nomura. 1977. Adequacy of survey data collected from substitute respondents. *American J. Epidemiol.* 106(6): 476-484.

Kornblith, P. L., M. D. Walker, and J. R. Cassody. 1987. Anatomic considerations. In *Neurologic Oncology*, 21-33. P. L. Kornblith, ed. Philadelphia, Pa.: J. B. Lippincott.

Lambe, M., P. Coogan, and J. Baron. 1997. Reproductive factors and the risk of brain tumors: A population-based study in Sweden. *Intl. J. Cancer* 72(3): 389-393.

Littorin, M., R. Attewell, S. Skerfving, V. Horstmann, and T. Moller. 1993. Mortality and tumour morbidity among Swedish market gardeners and orchardists. *Intl. Arch. Occup. Environ. Health* 65(3): 163-169.
McGranahan, D. A., J. C. Hession, F. K. Hines, and M. F. Jordan. 1986. Social and economic characteristics of the population in metro and nonmetro counties, 1970-1980. Rural development research reports. Washington, D.C.: USDA Economic Research Services.
McLaughlin, J. K., M. S. Dietz, E. S., Mehl, and W. J. Blot. 1987. Reliability of surrogate information on cigarette smoking by type of informant. *American J. Epidemiol.* 126(1): 144-146.
Morrison, H. I., R. M. Semenciw, D. Morison, S. Magwood, and Y. Mao. 1992. Brain cancer and farming in western Canada. *Neuroepidemiology* 11(4-6): 267-276.
Musicco, M., G. Filippini, B. M. Bordo, A. Melotto, G. Morello, and F. Berrino. 1982. Gliomas and occupational exposure to carcinogens: case-control study. *American J. Epidemiol.* 116(5): 782-790.
Musicco, M., M. Sant, S. Molinari, G. Filippini, G. Gatta, and F. Berrino. 1988. A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. *American J. Epidemiol.* 128(4): 778-785.
Muth, S. Q., J. J. Potterat, and R. B. Rothenberg. 2000. Birds of a feather: Using a rotational box plot to assess ascertainment bias. *Intl. J. Epidemiol.* 29(5): 899-904.
Ménégoz, F., J. Little, M. Colonna, A. Arslan, S. Preston-Martin, B. Schlehofer, M. Blettner, G. R. Howe, P. Ryan, G. G. Giles, Y. Rodvall, and W. N. Choi. 2002. Contacts with animals and humans as risk factors for adult brain tumours. An international case-control study. *European J. Cancer* 38(5): 696-704.
Nevitt, M. C., S. R. Cummings, W. S. Browner, D. G. Seeley, J. A. Cauley, T. M. Vogt, and D. M. Black. 1992. The accuracy of self-report of fractures in elderly women: Evidence from a prospective study. *American J. Epidemiol.* 135(5): 490-499.
NIOSH. 1995. National Institute for Occupational Safety and Health Worker Notification Procedures Manual (unpublished). Cincinnati, Ohio: NIOSH, Industrywide Studies Branch, Risk Communication Activity.
Percy, C., V. Van Holten, and C. Muir. 1990. *International Classification of Diseases for Oncology.* 2nd ed. Geneva, Switzerland: World Health Organization.
Pickle, L. W., L. M. Brown, and W. J. Blot. 1983. Information available from surrogate respondents in case-control interview studies. *American J. Epidemiol.* 118(1): 99-108.
Preston-Martin, S., B. E. Henderson, and L. Bernstein. 1985. Medical and dental x-rays as risk factors for recently diagnosed tumors of the head. *Nat. Cancer Inst. Monogr.* 69: 175-179.
Preston-Martin, S., W. Mack, and B. E. Henderson. 1989. Risk factors for gliomas and meningiomas in males in Los Angeles County. *Cancer Res.* 49(21): 6137-6143.
Rajmil, L., E. Fernandez, R. Gispert, M. Rue, J. P. Glutting, A. Plasencia, and A. Segura. 1999. Influence of proxy respondents in children's health interview surveys. *J. Epidemiol. Community Health* 53(1): 38-42.
Reif, J. S., N. Pearce, and J. Fraser. 1989. Occupational risks for brain cancer: a New Zealand Cancer Registry-based study. *J. Occup. Med.* 31(10): 863-867.
Robbins, J. M., C. M. Wolfson, H. Bergman, A. M. Clarfield, S. Kleiman, W. Bilker, and M. Baumgarten. 2000. Agreement between older subjects and proxy informants on history of surgery and childbirth. *J. American Geriatr. Soc.* 48(8): 975-979.
Rodvall, Y., A. Ahlbom, B. Spannare, and G. Nise. 1996. Glioma and occupational exposure in Sweden, a case-control study. *Occup. Environ. Med.* 53(8): 526-537.
Rosenberg, C. R., M. N. Mulvihill, A. Fischbein, and S. Blum. 1987. An analysis of the validity of self-reported occupational histories using a cohort of workers exposed to PCBs. *British J. Ind. Med.* 44(10): 702-710.
Rothman, K. J. 1981. Induction and latent periods. *American J. Epidemiol.* 114(2): 253-259.
Ruder, A. M., M. A. Waters, M. A. Butler, T. Carreón, G. M. Calvert, K. E. Davis-King, P. A. Schulte, W. Sanderson, E. M. Ward, L. B. Connally, E. F. Heineman, J. S. Mandel, R. F. Morton, D. J. Reding, K. D. Rosenman, G. Talaska, and the Brain Cancer Collaborative Study Group. 2006. Gliomas and farm pesticide exposure in men: The Upper Midwest Health Study. *Arch. Environ. Health* 59(12): (in press).

Ryan, P., M. W. Lee, B. North, and A. J. McMichael. 1992. Amalgam fillings, diagnostic dental x-rays, and tumours of the brain and meninges. *European J. Cancer B: Oral Oncol.* 28B(2): 91-95.
Salcman, M., and R. S. Kaplan. 1991. Intracranial tumors in adults. In *Comprehensive Textbook of Oncology*, 1339-1352. A. R. Moossa, S. C. Schimpff, and M. C. Robson, eds. Baltimore, Md.: Williams and Wilkins.
SAS. 1999. SAS System for Windows Release 8.00. Cary, N.C.: SAS Institute, Inc.
Schlehofer, B., S. Kunze, W. Sachsenheimer, M. Blettner, D. Niehoff, and J. Wahrendorf. 1990. Occupational risk factors for brain tumors: results from a population-based case-control study in Germany. *Cancer Causes Control* 1(3): 209-215.
Schlesselman, J. J. 1982. *Case-Control Studies: Design, Conduct, Analysis.* New York, N.Y.: Oxford University Press.
Semchuk, K. M., and E. J. Love. 1995. Effects of agricultural work and other proxy-derived case-control data on Parkinson's disease risk estimates. *American J. Epidemiol.* 141(8): 747-754.
Thelin, A., and S. Hoglund. 1994. Change of occupation and retirement among Swedish farmers and farm workers in relation to those in other occupations. A study of "elimination" from farming during the period 1970-1988. *Soc. Sci. Med.* 38(1): 147-151.
Torchio, P., A. R. Lepore, G. Corrao, P. Comba, L. Settimi, S. Belli, C. Magnani, and F. di Orio. 1994. Mortality study on a cohort of Italian licensed pesticide users. *Sci. Total Environ.* 149(3): 183-191.
Viel, J. F., B. Challier, A. Pitard, and D. Pobel. 1998. Brain cancer mortality among French farmers: The vineyard pesticide hypothesis. *Arch. Environ. Health* 53(1): 65-70.
Wacholder, S., B. Armstrong, and P. Hartge. 1993. Validation studies using an alloyed gold standard. *American J. Epidemiol.* 137(11): 1251-1258.
Walker, A. M., J. P. Velema, and J. M. Robins. 1988. Analysis of case-control data derived in part from proxy respondents. *American J. Epidemiol.* 127(5): 905-914.
Walker, M., A. G. Shaper, and D. G., Cook. 1987. Non-participation and mortality in a prospective study of cardiovascular disease. *J. Epidemiol. Community Health* 41(4): 295-299.
Weitzner, M. A. 1999. Psychosocial and neuropsychiatric aspects of patients with primary brain tumors. *Cancer Invest.* 17(4): 285-291.
Wingren, G., and O. Axelson. 1992. Cluster of brain cancers spuriously suggesting occupational risk among glassworkers. *Scandinavian J. Work Environ. Health* 18(2): 85-89.
Wrensch, M., M. Lee, R. Miike, B. Newman, G. Barger, R. Davis, J. Wiencke, and J. Neuhaus. 1997. Familial and personal medical history of cancer and nervous system conditions among adults with glioma and controls. *American J. Epidemiol.* 145(7): 581-593.

Appendix 1: UMHS Collaborators

The following lists group the UMHS collaborators by their professional affiliations at the time of the study:

National Institute for Occupational Safety and Health

Mary Ann Butler, PhD
Geoffrey Calvert, MD, MPH
Tania Carreón Valencia, PhD
Barbara Connally, MS
Karen Davis-King, MPH
John M. Fajen, MS
Everett Lehman, MS
A. Joan Levine, PhD
Martin Petersen, PhD
Avima M. Ruder, PhD

National Institute for Occupational Safety and Health (continued)

Wayne T. Sanderson, PhD
Teresa Schnorr, PhD
Paul A. Schulte, PhD
David Wall, MAS
Elizabeth M. Ward, PhD
Martha A. Waters, PhD, CIH
Zachary Zivkovich

The National Cancer Institute

Ellen Heineman, PhD

Louisiana State University

James Nelson, MD

Marshfield Clinic

Douglas Reding, MD, MPH, FACP
Karen Lappe, RN

Mercy Medical Center-Des Moines

Roscoe Morton, MD, FACP
Joann Muldoon, MS, MA

Michigan State University

Kenneth R. Rosenman, MD, MPH
Mary Jo Reilly, MS
Amy Sims

The United States Air Force

Timothy Irby, DVM

The University of Cincinnati

Glenn Talaska, PhD
Rick Hornung, PhD
Matthew Leary

The University of Minnesota

Jack Mandel, PhD, MPH
Rebecca A. Johnson, PhD
Teresa Hillmer, PhD
George Maldonado, PhD
Diane Kampa, BSB

Battelle

Diana Echeverria, PhD
Nicholas Heyer, PhD

Appendix 2: Classification Scheme for Counties

The basic unit of designation is metropolitan and non-metropolitan. More than one county may encompass a metropolitan area; thus, counties are further divided into core or fringe-suburban. Classifications are based on data from the 1980 Census.

Categories whose residents were not eligible for the study:

1 = Core counties more than 1 million.
2 = Fringe counties more than 1 million.
3 = Core of Standard Metropolitan Statistical Areas (SMSAs) 750,000 to 999,999.
4 = Fringe of SMSAs 750,000 to 999,999.
5 = Core of SMSAs 500,000 to 749,999.
6 = Fringe of SMSAs 500,000 to 749,999.
7 = Core of SMSAs 250,000 to 499,999.
8 = Fringe of SMSAs 250,000 to 499,999.

Categories whose residents were eligible for the study:

9 = Core of SMSAs 100,000 to 249,999.
10 = Fringe of SMSAs 100,000 to 249,999.
11 = SMSAs of 99,999 or less.
12 = Non-metropolitan, non-adjacent counties, size of largest place 10,000+.
13 = Non-metropolitan, adjacent counties, size of largest place 2500 to 9999.
14 = Non-metropolitan adjacent counties, size of largest place less than 2500.
15 = Non-metropolitan, non-adjacent counties, size of largest place 10,000+.
16 = Non-metropolitan, non-adjacent counties, size of largest place 2500 to 9999.
17 = Non-metropolitan non-adjacent counties, size of largest place less than 2500.

Eligible counties:

Iowa				
Adair	Clarke	Guthrie	Louisa	Poweshiek
Adams	Clay	Hamilton	Lucas	Ringgold
Allamakee	Clayton	Hancock	Lyon	Sac
Appanoose	Clinton	Hardin	Madison	Shelby
Audubon	Crawford	Harrison	Mahaska	Sioux
Benton	Dallas	Henry	Marion	Story
Black Hawk	Davis	Howard	Marshall	Tama
Boone	Decatur	Humboldt	Mills	Taylor
Bremer	Delaware	Ida	Mitchell	Union
Buchanan	Des Moines	Iowa	Monona	Van Buren
Buena Vista	Dickinson	Jackson	Monroe	Wapello
Butler	Dubuque	Jasper	Montgomery	Washington
Calhoun	Emmet	Jefferson	Muscatine	Wayne
Carroll	Fayette	Johnson	O'Brien	Webster
Cass	Floyd	Jones	Osceola	Winnebago
Cedar	Franklin	Keokuk	Page	Winneshiek
Cerro Gordo	Fremont	Kossuth	Palo Alto	Woodbury
Cherokee	Greene	Lee	Plymouth	Worth
Chickasaw	Grundy	Linn	Pocahontas	Wright
Michigan				
Alcona	Charlevoix	Huron	Mason	Otsego
Alger	Cheboygan	Iosco	Mecosta	Presque Isle
Allegan	Chippewa	Iron	Menominee	Roscommon
Alpena	Clare	Isabella	Midland	Saginaw
Antrim	Crawford	Jackson	Missaukee	St. Joseph
Arenac	Delta	Kalkaska	Montcalm	Sanilac
Baraga	Dickinson	Keweenaw	Montmorency	Schoolcraft
Barry	Emmet	Lake	Muskegon	Tuscola

Michigan (continued)				
Bay	Gladwin	Leelanau	Newaygo	Washtenaw
Benzie	Gogebic	Lenawee	Oceana	Wexford
Berrien	Grand Traverse	Luce	Ogemaw	
Branch	Gratiot	Mackinac	Ontonagon	
Calhoun	Hillsdale	Manistee	Osceola	
Cass	Houghton	Marquette	Oscoda	
Minnesota				
Aitkin	Douglas	Lake	Norman	Stearns
Becker	Faribault	Lake of the Woods	Olmsted	Steele
Beltrami	Fillmore	Le Sueur	Otter Tail	Stevens
Benton	Freeborn	Lincoln	Pennington	Swift
Big Stone	Goodhue	Lyon	Pine	Todd
Blue Earth	Grant	McLeod	Pipestone	Traverse
Brown	Houston	Mahnomen	Polk	Wabasha
Carlton	Hubbard	Marshall	Pope	Wadena
Cass	Isanti	Martin	Red Lake	Waseca
Chippewa	Itasca	Meeker	Redwood	Watonwan
Clay	Jackson	Mille Lacs	Renville	Wilkin
Clearwater	Kanabec	Morrison	Rice	Winona
Cook	Kandiyohi	Mower	Rock	Yellow Medicine
Cottonwood	Kittson	Murray	Roseau	
Crow Wing	Koochiching	Nicollet	Sherburne	
Dodge	Lac Qui Parle	Nobles	Sibley	
Wisconsin				
Adams	Dunn	Kenosha	Oneida	Shawano
Ashland	Eau Claire	Kewaunee	Ozaukee	Sheboygan
Barron	Florence	La Crosse	Pepin	Taylor
Bayfield	Fond du Lac	Lafayette	Pierce	Trempealeau
Brown	Forest	Langlade	Polk	Vernon
Buffalo	Grant	Lincoln	Portage	Vilas
Burnett	Green	Manitowoc	Price	Walworth
Chippewa	Green Lake	Marathon	Racine	Washburn
Clark	Iowa	Marinette	Richland	Waupaca
Columbia	Iron	Marquette	Rock	Waushara
Crawford	Jackson	Menominee	Rusk	Wood
Dodge	Jefferson	Monroe	Sauk	
Door	Juneau	Oconto	Sawyer	