Reproductive Factors and Risk of Glioma in Women

Kui Huang,[1] Elizabeth A. Whelan,[1] Avima M. Ruder,[1] Elizabeth M. Ward,[1] James A. Deddens,[1,2] Karen E. Davis-King,[1] Tania Carreón,[1] Martha A. Waters,[1] Mary Ann Butler,[1] Geoffrey M. Calvert,[1] Paul A. Schulte,[1] Zachary Zivkovich,[1] Ellen F. Heineman,[3] Jack S. Mandel,[4] Roscoe F. Morton,[5] Douglas J. Reding,[6] Kenneth D. Rosenman,[7] and The Brain Cancer Collaborative Study Group

[1]National Institute for Occupational Safety and Health, Cincinnati, Ohio; [2]Department of Mathematical Sciences, University of Cincinnati, Cincinnati, Ohio; [3]National Cancer Institute, Rockville, Maryland; [4]University of Minnesota, Minneapolis, Minnesota; [5]Mercy Medical Center, Des Moines, Iowa; [6]Marshfield Foundation, Marshfield, Wisconsin; and [7]Michigan State University, East Lansing, Michigan

Abstract

Objective: Glioma is the most common primary malignant brain tumor in adults, responsible for 75% of adult primary malignant brain tumors, yet aside from its association with ionizing radiation, its etiology is poorly understood. Sex differences in brain tumor incidence suggest that hormonal factors may play a role in the etiology of these tumors, but few studies have examined this association in detail. The objective of this study was to explore the role of reproductive factors in the etiology of glioma in women. Method: As part of a population-based case-control study, histologically confirmed primary glioma cases (n = 341 women) diagnosed between January 1, 1995 and January 31, 1997 were identified through clinics and hospitals in four Midwest U.S. states. Controls (n = 527 women) were randomly selected from lists of licensed drivers and Health Care Finance Administration enrollees. In-person interviews with subjects (81%) or their proxies (19%) collected reproductive history and other exposure information. Results: Glioma risk increased with older age at menarche (P for trend = 0.009) but only among postmenopausal women. Compared with women who never breast-fed, women who breast-fed >18 months over their lifetime were at increased risk of glioma (odds ratio, 1.8; 95% confidence interval, 1.1-2.9). Women who reported using hormones for symptoms of menopause had a decreased risk of glioma compared with women who never used such hormones (odds ratio, 0.7; 95% confidence interval, 0.5-1.1). Conclusion: These results support the hypothesis that reproductive hormones play a role in the etiology of glioma among women. (Cancer Epidemiol Biomarkers Prev 2004;13(10):1583–8)

Introduction

Sex differences in brain tumor incidence suggest that hormonal factors may play a role in the etiology of these tumors. The incidence of glioma is ~1.5 times greater in men than in women, whereas the incidence of meningioma is 1.5 times greater in women than in men (1). The overall objective of the current study, a case-control study of glioma in four Midwest U.S. states, was to investigate rural and farming-related exposures; a secondary objective was to explore reproductive factors, including use of exogenous hormones, in the etiology of glioma in women.

Glioma is the most common primary malignant brain tumor in adults, responsible for 75% of adult malignant primary brain tumors (2), yet aside from its association with ionizing radiation (3), its etiology is poorly understood. Several studies have described the sex differences in glioma incidence. In the United States, the male excess of glioma, apparent even during childhood and adolescence, increases with age (1). McKinley et al. (4), studying glioblastoma multiforme incidence in New York State in 1970 to 1995, reported that the protection afforded by being female does not emerge until ages 10 to 14 years, coinciding roughly with the onset of menstruation; is maximal at ages 50 to 54 years, when the incidence of glioblastoma multiforme in females is 50% of that in males; and seems to diminish later in life. Preston-Martin (5) found similar sex differences in analyses of glioma incidence among Blacks, Spanish-surnamed Whites, other Whites, and Asians/other groups in Los Angeles County in 1972 to 1985. Although data on international variation in glioma incidence are not readily available, variations in total brain tumor incidence largely reflect differences in glioma, and a similar pattern of male predominance is seen throughout the world (6). Age-specific incidence patterns of glioma in men and women in Sweden are nearly identical to those observed in the United States (7). The persistence of the sex difference across ethnic groups and in international comparisons suggests that intrinsic rather than environmental factors that differ between men and women are responsible. Such factors could be related to a protective effect of female hormones or to a deleterious effect mediated by male hormones.

No prior study has comprehensively examined the relationship between reproductive factors and the risk of glioma including use of exogenous hormones, breast-feeding, menstrual cycle patterns, menopausal status,

Received 2/3/04; revised 5/4/04; accepted 5/11/04.

Grant support: National Institute for Occupational Safety and Health Initiative for Cancer Control Projects for Farmers.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Requests for reprints: Elizabeth A. Whelan, Industrywide Studies Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, 4676 Columbia Parkway, R-15, Cincinnati, OH 45226. Phone: 513-841-4437; Fax: 513-841-4486. E-mail: EWhelan@cdc.gov

and the cumulative number of menstrual cycles over the lifetime prior to diagnosis. We evaluated the possible association between different aspects of reproductive history and primary brain glioma among women in a large case-control study conducted in four Midwest U.S. states.

Materials and Methods

Study Design and Subjects. The Upper Midwest Health Study is a population-based case-control study of primary glioma among residents of nonurban counties in Iowa, Michigan, Minnesota, and Wisconsin. Details of the design of this study have been described elsewhere.[8] Briefly, cases were identified through a network of clinics and hospitals in the four states. Eligible cases were ages 18 to 80 years with newly diagnosed primary intracranial glioma (*International Classification of Diseases for Oncology* codes 938-948) between January 1, 1995 and January 31, 1997 and were residents in nonurban areas of the states. Controls were randomly selected from lists of licensed drivers and from Health Care Finance Administration rolls of the states and frequency matched using the glioma distribution by sex and age at diagnosis during a 3-year period (1989-1992) in the four study states. The nonurban residence criterion applied to cases at the time of diagnosis and to controls at the time of control selection. Cases or controls with a prior malignancy other than a glioma were not excluded. The study was approved by the National Institute for Occupational Safety and Health Human Subjects Review Board and the institutional review boards from all participating institutions and 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) to safeguard individuals and establishments against invasions of privacy. All participants signed an informed consent on enrollment.

Data Collection. Between January 1995 and September 1998, trained staff conducted in-home interviews with participants or with proxies if the participant was deceased or incapacitated. The interview collected detailed information on demographic factors, residential history, occupational history, lifestyle factors, family history, and menstrual/reproductive history. Information was collected on potential risk factors through January 1993. This date was used as a cutoff date because more recent exposures may not be as relevant to etiology and the date represented the beginning of a new presidential term, a life event that respondents likely would recall. Menstrual and reproductive events included age at first menstrual period, age at last menstrual period, reason why periods stopped, periodicity of menstrual cycles (nearly always regular, generally regular, or irregular), history of infertility, number of pregnancies and outcome of each, and length of time each child was breast-fed. Information about the use of exogenous hormones, the reason(s) for use, the starting date, and total duration of use was also obtained. Twins or triplets (1% of all pregnancies) were counted as single births. Age at last birth was analyzed among all births as well as among women with two or more births.

A woman was considered postmenopausal if she reported natural menopause or hysterectomy with a bilateral oophorectomy before 1993. Women who reported hysterectomy without bilateral oophorectomy and who were ages >55 years in 1993 were also considered to be postmenopausal. Age 55 years was chosen because 90% of the study population had reached natural menopause by this age. Women who could not recall their exact age at menarche or menopause were asked to select an age range as an alternative. For these women, the midpoint of the age range was used as the estimated age for the event. This estimation method was used for age at menarche in 76 participants (9.7%) and for age at menopause in 61 participants (12.2 %).

A variable for lifetime menstrual activity, ''menstruation months,'' was created as a crude estimate of cumulative exposure to endogenous female hormones. This variable was calculated as the total number of months between the age at first menstrual period and the age at last menstrual period (or age in 1993 if premenopausal), subtracting 9 months for each live birth, the total number of months of breast-feeding, and the total number of months of oral contraceptive use. If any of the component variables was missing, then menstruation months were considered missing for that individual.

Statistical Analysis. Estimates of association between reproductive factors and glioma were made using unconditional logistic regression models, which generated odds ratios (OR) and 95% confidence intervals (95% CI). Natural cut points rather than percentiles were used to form categories. A variable was considered a confounder if removal of the variable from the model resulted in a change in the β estimate for the variable of interest of >15%. All estimates were adjusted for a quadratic effect of age in 1993. Statistical analyses were conducted using SAS software version 8.0 (8). All results were conducted both including and excluding proxy respondents. All statistical tests were two sided.

Results

Participation rates and characteristics of nonparticipants for the study overall are provided elsewhere.[8] In brief, the study included 873 eligible cases and 1,670 eligible controls. Of these, 799 cases or their proxies (92%) and 1,175 controls (70%) participated. Of 1,115 eligible women, 868 women or their proxies agreed to participate in the study (91% of cases and 72% of controls). Of these, 341 were histologically confirmed glioma cases and 527 were controls. Among participants, 57% of cases and 97% of controls were direct respondents and the remainder was proxy respondents. The majority of proxy respondents were spouses (56%). Table 1 provides demographic characteristics of study participants. Cases were, on average, younger than the controls ($P \leq 0.0005$). Cases were more likely than controls to have a first-degree relative with brain cancer ($P = 0.003$) when proxy respondents were included. Controls were more likely than cases to be postmenopausal as of 1993 ($P = 0.06$,

[8] A.M. Ruder et al. The Upper Midwest Health Study: a case-control study of primary intracranial brain gliomas among rural residents. Farm residence and glioma, submitted for publication.

Table 1. Selected characteristics of women in the Upper Midwest Health Study (age adjusted)

	Including proxies			Excluding proxies		
	Cases (n = 341)	Controls (n = 527)	P	Cases (n = 195)	Controls (n = 513)	P
Age in 1993 (y; mean ± SD)	52.0 ± 16.1	55.9 ± 15.9	0.0005	46.1 ± 15.4	55.5 ± 15.8	<0.0001
State of residence (%)						
Iowa	22.3	27.1	0.08	24.1	26.1	0.58
Michigan	33.4	25.2		31.3	25.3	
Minnesota	19.7	22.0		21.0	22.4	
Wisconsin	24.6	25.6		23.6	26.1	
Type of glioma (%)						
Glioma	5.6			6.7		
Astrocytoma	27.4			27.8		
Glioblastoma	53.1			43.3		
Oligodendroglioma	13.0			20.6		
Medulloblastoma/primitive neuroectodermal tumor	0.9			1.6		
Body mass index (kg/m^2; mean ± SD)	25.0 ± 5.2	24.8 ± 4.5	0.63	25.2 ± 5.3	24.9 ± 4.5	0.59
White (%)	98.2	98.5	0.97	98.5	98.6	0.93
Education (y; %)						
<12	15.3	14.8	0.37	8.7	14.2	0.90
12-15	69.4	71.4		73.3	71.5	
≥16	15.3	13.8		18.0	14.2	
Ever married (%)	91.8	93.4	0.75	89.2	93.2	0.36
First-degree relative with brain cancer (%)	7.0	3.1	0.003	3.2	3.0	0.62
Postmenopausal in 1993 (%)	47.7	66.3	0.06	36.6	65.7	0.02

NOTE: All statistical tests were two sided and P values were based on age-adjusted analyses.

including proxies). Other characteristics such as body mass index, race, education, and marital status were similar between cases and controls. In multivariate analyses, only age and menopausal status were determined to be important confounding variables.

Table 2 provides age-adjusted risk estimates for glioma and age at first menstruation, which was dependent on menopausal status. Cases were more likely than controls to have a later age at menarche (P for trend = 0.009 for model including proxies) but only among postmenopausal women. In this group, cases were 1.6 times more likely than controls to experience menarche after age 14 years. A total of 69 women (64 cases and 5 controls) were missing information on menopause and menarche. Using all the available data, stratified on age (<55 and ≥55 years) as a marker of presumed menopausal status, the results were similar but the interaction term was no longer statistically significant (P = 0.20).

Glioma cases were slightly more likely than controls to have had a live birth (including proxies, OR, 1.2; 95% CI, 0.8-2.0; Table 3), but there was no trend with increasing number of live births. Consistent trends in glioma risk were not observed with age at first or last (before 1993) live birth. Cases were slightly less likely than controls to have a history of miscarriage or induced abortion (including proxies, OR, 0.8; 95% CI, 0.6-1.2).

Table 2. Age at menarche and risk of glioma for women in the Upper Midwest Health Study, adjusted for age in 1993 and stratified by menopausal status

Including proxy respondents	Premenopausal			Postmenopausal		
	Cases (n = 145)	Controls (n = 177)	Adjusted OR (95% CI)	Cases (n = 132)	Controls (n = 346)	Adjusted OR (95% CI)
Age at menarche (y)						
<12	23	30	0.91 (0.49-1.68)	9	58	0.48 (0.22-1.01)
12-14	96	117	1.00	70	222	1.00
>14	11	20	0.67 (0.30-1.49)	18	35	1.62 (0.86-3.05)*
Excluding proxy respondents	Cases (n = 123)	Controls (n = 177)	Adjusted OR (95% CI)	Cases (n = 71)	Controls (n = 336)	Adjusted OR (95% CI)
Age at menarche (y)						
<12	22	30	1.02 (0.54-1.91)	4	57	0.31 (0.11-0.90)
12-14	82	117	1.00	48	218	1.00
>14	10	20	0.71 (0.31-1.64)	13	35	1.71 (0.83-3.51)†

NOTE: 69 women (64 cases and 5 controls) were missing information on menopausal status.
*P for trend = 0.009.
†P for trend = 0.005.

Table 3. Reproductive factors and risk of glioma for women in the Upper Midwest Health Study

	Including proxies			Excluding proxies		
	Cases*	Controls	Adjusted OR (95% CI)	Cases	Controls	Adjusted OR (95% CI)
Ever had a live birth						
No	42	84	1.00	30	83	1.00
Yes	235	438	1.22 (0.77-1.96)	164	430	1.21 (0.69-2.10)
No. live births						
0	42	84	1.00	30	83	1.00
1-2	99	158	1.22 (0.74-2.01)	77	156	1.19 (0.66-2.14)
>3	136	280	1.23 (0.74-2.04)	87	274	1.23 (0.67-2.24)
Age at first birth						
<20	67	113	1.00	43	112	1.00
20-24	115	237	0.85 (0.58-1.24)	79	233	0.90 (0.57-1.43)
>25	51	88	0.97 (0.60-1.57)	41	85	1.24 (0.71-2.17)
Age at last birth						
<25	43	87	1.00	35	87	1.00
25-34	146	242	1.51 (0.96-2.36)	102	236	1.38 (0.83-2.27)
>34	45	109	1.32 (0.76-2.29)	26	109	1.21 (0.63-2.31)
History of miscarriage or induced abortion						
No	205	367	1.00	147	362	1.00
Yes	71	155	0.82 (0.59-1.15)	47	151	0.72 (0.48-1.08)
Age at natural menopause						
≤50	25	114	1.00	17	112	1.00
>50	18	80	1.07 (0.55-2.11)	15	79	1.35 (0.63-2.90)
Type of menopause						
Natural	72	218	1.00	44	212	1.00
Bilateral oophorectomy	32	63	1.48 (0.89-2.46)	14	61	1.07 (0.54-2.10)
Unilateral oophorectomy	42	82	1.36 (0.81-2.28)	24	81	0.98 (0.49-1.96)
Regular menstrual cycles at age 18-40 y						
No	53	96	1.00	42	95	1.00
Yes	206	417	0.90 (0.61-1.32)	149	409	0.79 (0.51-1.22)
Menstruation months						
≤330	123	200	1.00	104	200	1.00
331-438	58	170	0.75 (0.48-1.18)	46	166	0.96 (0.57-1.62)
>438	10	65	0.47 (0.21-1.03)	9	64	0.81 (0.35-1.91)
Ever breast-fed a child						
No	137	260	1.00	96	256	1.00
Yes	131	247	1.04 (0.77-1.42)	95	242	1.05 (0.73-1.50)
Duration of breast-feeding (mo)						
0	137	259	1.00	96	255	1.00
1-3	20	82	0.50 (0.29-0.87)	13	82	0.47 (0.24-0.90)
4-8	21	57	0.71 (0.41-1.25)	16	53	0.75 (0.40-1.43)
9-18	37	54	1.13 (0.69-1.83)	34	54	1.37 (0.81-2.31)
>18	40	49	1.77 (1.08-2.89)†	29	49	1.81 (1.03-3.20)†
Oral contraceptive use						
Never	187	394	1.00	128	385	1.00
Ever	72	127	0.83 (0.58-1.20)	63	127	0.93 (0.62-1.39)
Years of oral contraceptive use						
≤5	35	69	1.00	33	69	1.00
>5	33	51	1.02 (0.53-1.95)	29	51	0.92 (0.47-1.81)
Ever use of hormones for menopausal symptoms						
No	218	377	1.00	169	371	1.00
Yes	46	142	0.73 (0.49-1.10)	24	139	0.60 (0.36-0.99)
Total years used hormones for menopausal symptoms						
≤5	23	67	1.00	14	66	1.00
>5	18	67	0.88 (0.42-1.83)	9	67	0.68 (0.26-1.73)

NOTE: Adjusted for age in 1993, age × age, menopausal status, and age × menopausal status.
*Numbers do not always total to 100% because of missing data.
†P for trend = 0.006.

Cases were somewhat more likely than controls to have had surgical menopause but only when proxy respondents were included in the analysis (Table 3). Cases and controls were equally likely to report having regular cycles at ages 18 to 40 years, but cases were less likely than controls to have a high cumulative number of menstruation months (>438; OR, 0.5; 95% CI, 0.2-1.0; P for trend = 0.006). The latter finding was not observed when proxy respondents were excluded from the analysis.

Glioma cases and controls were equally likely to report ever breast-feeding a child (OR, 1.04; 95% CI, 0.8-1.4; Table 3), but cases were more likely than controls to report breast-feeding >18 months over their lifetime (including proxies, OR, 1.8; 95% CI, 1.1-2.9). This trend was statistically significant (P = 0.006). When breast-feeding was defined in terms of the average number of months each child was breast-fed rather than total duration, the same pattern was observed. The pattern also remained after adjustment for birth year of the child, in an attempt to take into account changes in U.S. trends in breast-feeding (data not shown). Because reproductive patterns such as breast-feeding may be different in rural women, we also adjusted for ever living or working on a farm and ever having had exposure to pesticides; results were unchanged.

There was little association between the use of oral contraceptives and glioma risk (Table 3). Cases were less likely than controls to report using hormones for symptoms of menopause (including proxies, OR, 0.7; 95% CI, 0.5-1.1). In the analysis excluding proxy respondents, cases were ~30% less likely than controls to report using hormone replacement for menopausal symptoms for >5 years (OR, 0.7; 95% CI, 0.3-1.7).

To examine potential differences in etiology by histologic tumor type, we reanalyzed the data using each of the four major histology types (glioma, astrocytoma, glioblastoma, and oligodendroglioma) as the case group compared with all controls. Overall, the pattern of results was the same (data not shown).

Discussion

Few studies have examined reproductive risk factors for brain tumors or gliomas in women; the only reproductive factor that has been examined in several studies is parity. Cohort studies of brain cancer mortality in relation to parity have shown inconsistent results and are of limited interest because they include meningiomas and other types of brain tumors likely to have different hormonal influences (9-11). A small, population-based case-control study of gliomas in Germany found no association with ever experiencing a pregnancy (12). Two other case-control studies reported that parous women were at reduced risk of glioma but having more than one child conferred little or no additional protection (7, 13). For one of these studies (7), the protective effect of parity was evident only in women of premenopausal age (≤50 years). Age at first birth was unrelated to risk. In a case-control study of glioma in Australia, parity seemed to be protective when proxy interviews were excluded (OR, 0.7; 95% CI, 0.3-1.5) but not when they were included (OR, 1.1; 95% CI, 0.6-2.1; ref. 14).

Overall, we found some suggestion for a role for reproductive factors in the development of brain cancer. Inverse associations were found with age at menarche (among postmenopausal women), menstruation months, and fewer months of breast-feeding—a pattern of associations that may be seen as the reverse of that observed for breast cancer (15). The use of hormone replacement therapy, which has been found to increase the risk of breast cancer (16), was associated with a decreased risk for glioma in our study. On the other hand, we saw little evidence for an association with parity or age at first birth, two established risk factors for breast cancer. The patterns we observed are consistent with a protective effect of female reproductive hormones on risk of glioma as suggested by the differences in sex-specific incidence rates.

The association with age at menarche differed between premenopausal and postmenopausal women and the proportion of premenopausal women among cases was higher than the proportion of premenopausal women among controls. The difference in menopausal status between cases and controls is primarily explained by their differing age distributions, because cases were more likely than controls to reach natural menopause at age >50 years. Unlike breast cancer, it has not been previously apparent that risk factors for brain cancer may differ for premenopausal and postmenopausal cases. Only one prior study (7) made an attempt to examine differences in glioma risk by menopausal status, finding a protective effect of parity only among women of premenopausal age (≤50 years). We found that increasing age at menarche was associated with glioma only among postmenopausal women. For breast cancer, it has been difficult to clearly elucidate the potential biological mechanism that underlies the patterns in risk observed by menopausal status. For brain cancer, it is even more difficult to speculate on the underlying biology that may explain these patterns.

Our finding that cases were more likely than controls to report breast-feeding for a long period of time was unexpected. However, as has been pointed out by other authors, it is difficult to disentangle the effects of a specific reproductive risk factor, such as breast-feeding, from the effects of other aspects of childbearing. For example, women breast-feed only after bearing a child, and the earlier they begin childbearing, the more children they have and the longer their duration of breast-feeding (17). The fact that the association with breast-feeding has been so difficult to discern for breast cancer despite extensive study (17, 18) emphasizes the importance of caution in interpreting the results of a single study showing this association for brain cancer.

If the association between duration of breast-feeding and risk of brain cancer is confirmed in subsequent studies, hypothesized mechanisms may be similar to those advanced for the protective effect of breast-feeding on breast cancer risk, including the hypothesis that lactation causes long-term endogenous hormonal changes, possibly reduced estrogen and increased prolactin production decreasing a woman's cumulative exposure to estrogen, or the role of breast-feeding in delaying the reestablishment of ovulation (18-21). In considering the possible mechanism for a more specific association between brain cancer and breast-feeding, a direct role for oxytocin and/or prolactin might also be considered.

Prolactin has been shown to cross the blood-brain barrier, and levels of prolactin in the cerebrospinal fluid are reported to parallel serum levels (22). In addition to its role in regulating mammary gland growth and lactation, prolactin is reported to stimulate cell growth in astrocytes (23).

Strengths of our study include the large number of histologically confirmed primary gliomas and the use of population-based controls. Exclusion of other brain malignancies, such as meningiomas, which are more common in women and have a suspected hormonal etiology, eliminated the variability associated with studying multiple cancer types. However, our study also had several limitations. Because controls were selected based on the age distribution of gliomas in the 3 years preceding the study, controls were, on average, older than the cases, necessitating age adjustment in all analyses. The age difference also meant that cases were less likely to have reached menopause by the end of the study period, necessitating adjustment for menopausal status as well in the analysis of reproductive risk factors. Missing information on age at menopause and age at menarche reduced the number of women (by $n = 69$) for whom the menstruation months variable could be calculated. Another limitation of the study is the collection of data for over 40% of the cases from proxy respondents. However, with the exception of the results for the variable menstruation months, the overall pattern of associations was the same for the models including and excluding proxy respondents. Although women were asked to recall pregnancy-related events that occurred decades earlier, studies have shown that most events, including breast-feeding duration, are accurately recalled (24).

In conclusion, this study provides suggestive evidence that hormones related to female reproductive function may be associated with brain cancer risk and highlights the importance of considering female reproductive history in studies of the etiology of brain cancer.

Acknowledgments

We thank the study participants, physicians and participating institutions, interviewers, phlebotomists, and field centers and the National Institute for Occupational Safety and Health staff who participated in protocol development, contract monitoring, data quality control, and data analysis.

References

1. Inskip PD, Linet MS, Heineman EF. Etiology of brain tumors in adults. Epidemiol Rev 1995;17:382–414.
2. Jukich PJ, McCarthy BJ, Surawicz TS, Freels S, Davis FG. Trends in the incidence of primary brain tumors in the United States, 1985–1994. Neuro-oncol 2001;3:141–51.
3. El-Zein R, Minn AY, Wrensch M, Bondy ML. Epidemiology of brain tumors. In: Levin VA, editor. Cancer in the nervous system. New York: Oxford University Press, Inc.; 2002. p. 252–66.
4. McKinley BP, Michalek AM, Fenstermaker RA, Plunkett RJ. The impact of age and sex on the incidence of glial tumors in New York state from 1976 to 1995. J Neurosurg 2000;93:932–9.
5. Preston-Martin S. Descriptive epidemiology of primary tumors of the brain, cranial nerves and cranial meninges in Los Angeles County. Neuroepidemiology 1989;8:283–95.
6. Parkin DM, Whelan SL, Ferlay J, et al., editors. Cancer incidence in five continents. Vol. 7. IARC Scientific Publications No. 143. Lyon (France): IARC; 1997.
7. Lambe M, Coogan P, Baron J. Reproductive factors and the risk of brain tumors: a population-based study in Sweden. Int J Cancer 1997;72:389–93.
8. SAS system for Windows release 8.00. Cary (NC): SAS Institute, Inc.; 1999.
9. Green A, Beral V, Moser K. Mortality in women in relation to their childbearing history. BMJ 1988;297:391–5.
10. Plesko I, Preston-Martin S, Day NE, Tzonou A, Dimitrova E, Somogyi J. Parity and cancer risk in Slovakia. Int J Cancer 1985;36:529–33.
11. Miller AB, Barclay THC, Choi NW, et al. A study of cancer, parity and age at first pregnancy. J Chronic Dis 1980;33:595–605.
12. Schlehofer B, Blettner M, Wahrendorf J. Association between brain tumors and menopausal status. J Nat Cancer Inst 1992;84:1346–9.
13. Cantor KP, Lynch CF, Johnson D. Reproductive factors and risk of brain, colon and other malignancies in Iowa (United States). Cancer Causes Control 1993;4:505–11.
14. Cicuttini FM, Hurley SF, Forbes A, et al. Association of adult glioma with medical conditions; family and reproductive history. Int J Cancer 1997;71:203–7.
15. Clavel-Chapelon F, E3N Group. Cumulative number of menstrual cycles and breast cancer risk: results from the E3N cohort study of French women. Cancer Causes Control 2002;13:831–8.
16. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
17. Collaborative Group on Hormonal Factors and Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. Lancet 2002;360:187–95.
18. Lipworth L, Bailey LR, Trichopoulos D. History of breastfeeding in relation to breast cancer risk: a review of the epidemiologic literature. J Natl Cancer Inst 2000;92:302–12.
19. Byers T, Graham S, Rzepka T, Marshall J. Lactation and breast cancer. Evidence for a negative association in premenopausal women. Am J Epidemiol 1985;12:664–74.
20. Key TJ, Pike MC. The role of estrogens and progestagens in the epidemiology and prevention of breast cancer. Eur J Cancer Clin Oncol 1988;24:29–34.
21. Henderson BE, Pike MC, Casagrande JT. Breast cancer and the estrogen window hypothesis. Lancet 1981;2:363–4.
22. Grattan DR. The actions of prolactin in the brain during pregnancy and lactation. Prog Brain Res 2001;133:153–71.
23. DeVito WJ, Okulicz WC, Stone S, Avakian C. Prolactin-stimulated mitogenesis of cultured astrocytes. Endocrinology 1992;130:2549–56.
24. Tomeo CA, Rich-Edwards JW, Michels KB, et al. Reproducibility and validity of maternal recall of pregnancy-related events. Epidemiology 1999;10:774–7.

Reproductive Factors and Risk of Glioma in Women

Kui Huang, Elizabeth A. Whelan, Avima M. Ruder, et al.

Cancer Epidemiol Biomarkers Prev 2004;13:1583-1588.