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Journal
Cancer Causes & Control, 25(8)

ISSN
0957-5243

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Publication Date
2014-08-01

DOI
10.1007/s10552-014-0400-8

Peer reviewed

Published in final edited form as:
Cancer Causes Control. 2014 August ; 25(8): 1007–1013. doi:10.1007/s10552-014-0400-8.

A Pooled Multisite Analysis of the Effects of Female Reproductive Hormones on Glioma Risk

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Abstract

Purpose—The association between female reproductive factors and glioma risk is unclear, but most published studies have been limited by small sample size. We conducted a pooled multisite study of pre- and post-menopausal women, investigating the effect of female reproductive factors, including hormonal medications.

Methods—Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals assessing the effects of female reproductive factors and female hormonal medications in glioma cases and unrelated controls.

Results—Menarche over the age of 15 as compared to under 12 was associated with a statistically significant risk for glioma (OR = 2.00, 95% CI, 1.47–2.71). Use of Oral Contraceptive Pills (OCP) was inversely associated with risk of glioma (OR= 0.61, 95% CI, 0.50–0.74) and there was an inverse trend with longer duration of OCP use (p for trend< 0.0001). Use of Hormone Replacement Therapy (HRT) was also inversely associated with risk of glioma (OR=0.55, 95% CI, 0.44–0.68) and there was an inverse trend with longer duration of use (p for trend< 0.0001). Compared to those reporting neither OCP use nor HRT use, those who reported using both were less likely to have a diagnosis of glioma (OR = 0.34, 95% CI, 0.24–0.48).

Conclusions—Female reproductive hormones may decrease the risk for glioma. The association appears to be strongest with greater length of use and use of both HRT and OCP.

Keywords

HRT; Hormones; Females; Contraceptives; Glioma

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Introduction

The broad category of glioma represents 30% of all primary brain tumors and 80% of all primary malignant brain tumors. Glioblastoma, a highly aggressive form of glioma, accounts for the majority of gliomas. Less than 5% of glioblastoma patients are still alive at 5 years after diagnosis [1]. The etiology of glioma is poorly established. Exposure to ionizing radiation is the only environmental factor consistently associated with increased glioma risk [2, 3]. Gender is also associated with glioma, with a higher incidence in males (7.10 per 100,000 person-years) than in females (5.01 per 100,000 person-years), suggesting that there may be hormonal influences in the development of glioma [1].

Biological studies show that steroid hormone receptors are expressed in normal and malignant glial cells [4–7]. However, epidemiological studies examining the association of female reproductive factors and/or female hormone exposure and exogenous hormone use with risk of glioma in women have yielded inconsistent results with no evidence of trends with increasing duration of hormone use [8–19]. Several of the published studies were limited by small sample size or limited exposure data. A recent meta-analysis reported a lower risk of glioma with use of oral contraceptives (RR = 0.71, 95% CI 0.60–0.83), use of hormone replacement therapy (RR= 0.68, 95% CI 0.58–0.81), and found an increased risk of glioma with older age of menarche (RR= 1.40, 95% CI: 1.05–1.87). However, they were unable to perform any dose-response or time dependent evaluations [20].

A prospective study evaluating the association between menstrual and reproductive factors, exogenous hormone use, and glioma risk among 225,355 women found that older age at menarche was positively associated with risk: (HR =1.67, 95% CI: 1.03, 2.69). Other reproductive factors, including age at first live birth, parity, age at menopause, type of menopause (natural vs. medical) and exogenous hormone use showed no association with glioma risk. The study strengths included the prospective nature of the study, evaluation of type of hormone used (estrogen and/or progesterone) and duration of hormone use, but the number of glioma cases was small [21].

To evaluate the associations between hormone use and glioma in a study sample with adequate statistical power, we created pooled data obtained from three separate institutions and populations.

Methods

Data were obtained from three separate case-control studies of glioma risk factors conducted by the University of Illinois at Chicago/Duke, the University of Texas MD Anderson Cancer Center (MDACC), and the University of California, San Francisco (UCSF). Institutional Review Board approvals were obtained from all institutions.

Study Population

UIC/Duke—Hospital-based glioma cases were identified from Duke and North Shore University Health System (NSUHS) during the period of August 2003 – April, 2008 with a pathologically confirmed new diagnosis (ICDO-3 sites C70.0-C72.9 and C75.1–C75.3) of

glioblastoma (ICDO-3 histology codes 9440–9442), non GBM-astrocytoma (9400–9411 and 9420–9421), or oligodendroglioma (9450–9460). Patients who were aged 18 years or older, English speaking, and residents of the United States were eligible for recruitment. After screening (n=1712), 1039 were determined as eligible to participate. Seven hundred forty-one patients consented to participate (participation rate=71%). Multiple friend controls, up to five, were recruited for each case. Friend controls had to be aged 18 years or older, could not be a blood relative or significant other of the case, had to reside in the United States, speak English, and could not have had a brain tumor. 81% of eligible friend controls participated in the study. Clinic-based controls were recruited from patients seen at Duke University (96% from orthopedic clinics and 4% from other clinics) and NSUHS (from neurology clinics). Clinic controls were aged 18 years or older, had to reside on the United States, and could not have had a brain tumor or history of a neurodegenerative disease, and were frequency matched to cases by age (10-year interval), gender, and race/ethnicity. 95% of eligible clinic controls participated in this study. Subjects who consented to participate were asked to complete a web-based or telephone survey that included information on demographics, personal and family medical history, as well as occupational, residential, dietary, and numerous potential environmental exposures.

MD ANDERSON CANCER CENTER—Using population-based methods, cases consisted of adults over the age of 18 years with newly diagnosed, pathologically confirmed glioma (ICD-O-3 codes 9380-9481) identified in the MDACC Neuro-Oncology clinic between January 2001 and January 2006 who live in several counties around Houston, Texas. Controls were obtained through a contracting company by random-digit dialing in the same geographic areas as the cases and were frequency-matched to cases on age (within 5 years), race/ethnicity and sex. The participation rate was 77% for cases and 53% for controls Questionnaires were used to conduct detailed in-person or telephone interviews on subjects or their proxies through which data on demographic factors, health characteristics, medications, reproductive factors and familial attributes were collected [22].

UCSF—Study subjects were recruited by population-based methods in the San Francisco Bay Area from 1997–2004. Cases included all individuals diagnosed with pathologically confirmed glioma (ICD codes 9380 to 9481) and were identified via rapid case ascertainment methods using the Northern California Cancer Registry. All cases and controls were 20 years of age or older. Population based controls were selected through random digit dialing and frequency matched to cases by age, race, and gender. Subjects or their proxies completed a detailed in-person interview and data were collected on demographic factors, health characteristics, medications and reproductive factors [23, 24]. The participation rate was 75% for cases and 73% for controls

Statistical Methods

Subjects in each study were asked about the following reproductive factors: menopausal status, age at menarche and age at menopause. Post-menopausal status was assessed by asking whether the subjects were still having a menstrual period or by asking whether they had reached menopause, and age at menopause was defined as the age when periods stopped. Subjects were also asked about the use of oral contraceptives (OCP) and hormone

replacement therapy (HRT), as well as the length of use of each medication. Data were analyzed for each institution separately and variables from each study were evaluated and recoded to a common dataset for use in a pooled analysis. Only females were included in this analysis.

Analyses were conducted using SAS version 9.1 (SAS Institute, Cary, NC). UIC/Duke cases and friend controls were un-matched for the analyses as they were matched initially only on their friendship status. This allowed use of cases lacking matched controls. Comparison of matched and unmatched analyses using the same study population demonstrated that un-matching did not introduce significant confounding. Data from UIC/Duke, UCSF and MDACC were analyzed separately and as a pooled dataset (data for individual institutions not shown). Data from UCSF and MDACC were analyzed separately for case data that was acquired through self-report, and data from all proxy and self-report cases combined to ensure that inclusion of proxy reports did not alter results (data not shown). Additionally, data was analyzed separately using cases from each histology group to ensure results were not heterogeneous between histology groups (data not shown). Associations between cases and controls were tested using a Chi-Square statistic for categorical variables and a t-test for continuous variables. Age-, institution- and race-adjusted odds ratios and their 95% confidence intervals (CIs) were estimated using unconditional logistic regression models. Calculation of p for trend was done by including years of OCP or HRT use in the model as a continuous variable. Statistical significance was assessed using a two sided test at the alpha=.05 level for all studies.

The UIC/Duke dataset initially included 288 female cases and 535 female controls. For the analysis including pre and post-menopausal women, one case and one hospital control were deleted due to missing responses for OCP use, resulting in a dataset with 287 cases and 534 controls. For the analyses including postmenopausal women only, two cases, one friend control and one hospital control were missing responses for use of HRT, and there were no missing responses for OCP use. After deleting individuals with missing responses, the UIC/Duke dataset for postmenopausal women had 174 cases and 350 controls.

The MDACC dataset had 276 cases and 348 controls. 91% of MDACC case data was obtained through self-report. For the analyses including postmenopausal women only, the MDACC dataset had 130 female cases and 187 female controls. No subjects were missing responses for OCP or HRT use. The total pooled dataset included 968 cases and 1322 controls. For the analyses including postmenopausal women only, the total pooled dataset included 549 cases and 805 controls.

The UCSF dataset had 415 female cases and 441 female controls. 70% of UCSF case data was obtained through self-report. For the analysis including pre and post-menopausal women, ten cases and one control were deleted due to missing responses for OCP use, resulting in a dataset with 405 cases and 440 controls. For the analyses including postmenopausal women only, nine cases and one control were missing responses for use of HRT, and six cases and one control missing responses for OCP use. After deleting individuals with missing responses, the UCSF dataset for postmenopausal women had 245 cases and 268 controls. An initial analysis was conducted looking at all women for all

variables except those variables relating only to post-menopausal women. A separate analysis was conducted using only post-menopausal women to investigate the effects of age at menopause, as well as HRT use.

Results

As shown in Table 1, the analyses involving both pre- and post-menopausal women resulted in 968 cases and 1322 controls. The mean age of cases and controls were similar (51.4 vs 52.5 years). There was no statistically significant difference between cases and controls in racial distribution. A little over half of the cases (52.8%) were glioblastomas.

Table 2 shows the magnitude of the associations between endogenous female reproductive factors and exogenous hormonal medications and glioma in pre- and post-menopausal women combined, controlling for age, race, and institution. Premenopausal status was not associated with risk of glioma. Menarche over the age of 15 as compared to under 12 was associated with a statistically significant risk for glioma (OR = 2.00, 95% CI, 1.47–2.71). Use of OCP was inversely associated with risk of glioma (OR= 0.61, 95% CI, 0.50–0.74). The inverse association became more pronounced with longer duration of OCP use (p for trend< 0.0001). More than ten years of OCP use as compared to no use was associated with the lowest odds ratio (OR = 0.49 [95% CI, 0.37–0.66]).

Table 3 shows the magnitude of the associations between endogenous female reproductive factors and exogenous hormonal medications and glioma in post-menopausal women, controlling for age, race, and institution. Age at menopause was not significantly associated with glioma risk. Use of OCP was inversely associated with glioma (OR=0.58, 95% CI, 0.45, 0.75). The inverse association became more pronounced with greater years of OCP use except at 6–10 years use, where the OR was higher (OR=0.80, 95% CI, 0.54–1.19) than it was with 1–5 years of use (OR=0.67, 95% CI, 0.49, 0.92). The over-all trend was still significant (p for trend= 0.001). Use of HRT was also inversely associated with risk of glioma (OR=0.55, 95% CI, 0.44–0.68). The inverse association became more pronounced with greater years of HRT use (p for trend< 0.0001).

Table 4 shows the magnitude of the associations between gliomas and use of both OCP and HRT in post-menopausal women. Compared to those reporting neither OCP use nor HRT use, those who reported using both were less likely to have a diagnosis of glioma (OR = 0.34, 95% CI, 0.24–0.48).

DISCUSSION

In this study, female hormonal medication use (both OCP and HRT) were less prevalent among cases than controls. Longer duration of use of hormonal medications was inversely associated with glioma risk, and use of both OCP and HRT exhibited a greater inverse association than use of either hormonal medication alone. Longer duration of use of OCP was inversely associated with glioma risk even in post-menopausal women, suggesting there may be a long-lasting protective effect with exogenous female hormone use. In our study, pre-menopausal status and age at menopause were not associated with gliomas. However,

menarche over the age of 15 as compared to under age 12 was associated with a statistically significant risk for glioma.

Several studies have been published investigating the effects on female reproductive factors on risk of glioma, yielding inconsistent results [4,8,9,14, 16,19, 20]. Qi et al. used 11 eligible studies with 4860 cases and 14,740 controls to conduct a meta-analysis and found a lower risk of glioma among women who were ever users of exogenous hormones (OC RR = 0.707, 95% CI = 0.604–0.828; HRT: RR = 0.683, 95% CI = 0.577–0.808) compared with never users. They also found an increased glioma risk with older age at menarche (RR = 1.401, 95% CI = 1.052–1.865). They observed no association for menopause status, parous status, age at menopause, or age at first birth and glioma risk. They concluded that female sex hormones play a role in the development of glioma [20].

The mechanism whereby hormonal medication use might affect glioma risk is unknown, but modulation of the human immune system may be one possibility [25]. Immune reactions in the body are typically classified as being either pro-inflammatory (Th1) or anti-inflammatory (Th2). Th2-type cytokines promote IgE antibody production, which is one of the features of atopic medical conditions, including allergies, asthma and eczema [26]. Several epidemiological studies have found that Th2 type promoting atopic conditions are associated with a protective effect in glioblastoma [27,28]. Like atopic conditions, reproductive hormones may also be associated with a Th2 response. Cells related to the immune system express estrogen receptors, and a study that looked at the cytokine profiles in the serum of men and women found that females express a predominantly Th2 profile [29]. An animal model of Th1 autoimmune disease showed that estrogen is protective through its effect on decreasing Th1 cytokines [30]. Clinical trials and histological evidence also lend support to the idea that female reproductive hormones are most likely associated with a Th2 immune profile [31–37].

A strength of this analysis included the availability of a large number of variables related to female reproductive hormones for study, several of which are poorly studied with respect to glioma. Additionally, the ability to pool studies greatly increased sample size. There were weaknesses in the study as well. Self-reported data is always at risk for being affected by recall bias. It should also be noted that the definition of hormonal medication was broad, since there may be several different varieties of both OCP and HRT, and none of the surveys distinguished between these varieties of medications. The conflicting results in published literature regarding the effects of female hormones on glioma risk may be a result of failure to account for medication dosage or length of hormone use. Future studies should address these weaknesses, and focus on the specific pharmacological properties of specific medications in conjunction with their effects on glioma risk.

Other weaknesses also need to be considered when considering the conclusions of this study. Selection bias is a possibility due to control non-participation. Additionally, we did not have access to several socio-demographic variables and could thus not assess whether participating controls had a higher socioeconomic status (SES) than non-participating controls. This may be an issue as higher SES may be related to greater OCP or HRT use. Hormone based medications are also associated with a great variety of health conditions and

health behaviors that are difficult to control for and that were not addressed in this analysis. Finally, our study encompassed different healthcare systems and states and thus additional biases may have been introduced by varying physician prescription patterns and insurance coverage and use of specific medications between states and medical systems.

Despite the study weaknesses, these data add to the evidence of a reduced risk for glioma, showing cases have lower prevalence of female reproductive hormones use than controls. Clarification of these observations and the mechanisms underlying these observations is needed.

Acknowledgments

Financial Support: Research at the University of Illinois at Chicago was conducted under an NIH grant (5P50 CA108786-4), directed by Faith Davis, PhD. Funding was also received from the American Brain Tumor Association. Data from MD Anderson Cancer Center was collected under two separate NIH grants, directed by Melissa Bondy, PhD (R01CA070917) and Michael Scheurer, PhD (R01CA070917). Data from UCSF was collected with funding from two NIH grants, directed by Margaret Wrensch, PhD (R01CA52689 and P50CA097257).

Grant Funding:

Research at the University of Illinois at Chicago was conducted under a Brain Tumor SPORE grant project (NIH Specialized Programs of Research Excellence grant 5P50 CA108786-4), directed by Dr. Faith Davis, Dr. Darell Bigner and Dr. Francis Ali-Osman. Funding was also received from the American Brain Tumor Association. Data from MD Anderson Cancer Center was collected under NIH grant R01CA070917 (M. Bondy, PI). M. E. Scheurer was funded by NIH grant K07CA131505. Data from UCSF was collected with funding from R01CA52689 and P50CA097257

The Brain Tumor Epidemiology Consortium (BTEC) was instrumental in facilitating the collaboration and data sharing necessary for this study. In addition, the following individuals are acknowledged for their contributions: MD Anderson: Phyllis Adatto; University of Illinois at Chicago/Duke Study: Candace Zahora, Kristin Rankin, North Shore University Health System: Pat Lada, and Nicholas Vick; University of California at San Francisco: Lucie McCoy and Terri Rice.

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Cancer Causes Control. Author manuscript; available in PMC 2015 January 09.

Table 1

Distribution of Demographic Characteristics for All Female Glioma Cases and Controls From Three US Studies [a]

	UCSF			UIC/Duke			MDACC			Pooled Analysis[a]		
Variable	**Cases N=405**	**Controls N=440**	**p-value**	**Cases N=287**	**Controls N=534**	**p-value**	**Cases N=276**	**Controls N=348**	**p-value**	**Cases N=968**	**Controls N=1322**	**p-value**
Age	55.4 (SD 16.7)	54.6 (SD 16.3)	0.46	48.7 (SD 13.4)	52.9 (SD 14.1)	<0.0001	48.4 (SD 13.6)	49.2 (SD 13.5)	0.49	51.4 (SD 15.3)	52.5 (SD14.9)	0.09
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
Race: white	310 (76.5%)	344 (78.2%)	0.57	264 (92.0%)	477 (89.3%)	0.20	227 (82.3%)	296 (85.1%)	0.34	801 (82.8%)	1117 (84.5%)	0.26
Glioblastoma	235 (58.0%)	NA	NA	129 (45.2%)	NA	NA	145 (52.5%)	NA	NA	509 (52.8%)	NA	NA
Non-GBM Astrocytoma	75 (18.5%)	NA	NA	89 (31.3%)	NA	NA	52 (18.8%)	NA	NA	216 (22.4%)	NA	NA
Oligodendroglioma	47 (11.6%)	NA	NA	56 (19.7%)	NA	NA	50 (18.1%)	NA	NA	153 (15.9%)	NA	NA

[a] UCSF, UIC/Duke and MDACC and Pooled Study of all Institutions Combined

Table 2

Associations in All Females Between Reproductive Factors or Hormonal Medications and Gliomas: Pooled Data From Three US Studies [a]

Variable	Cases N=968 (%)	Controls N=1322 (%)	OR (95% CI)[b]	p-value
Endogenous Hormonal Factors				
Post-menopausal	557 (57.5)	806 (61.0)	REF	
Pre-menopausal	401 (41.4)	513 (38.8)	1.02 (0.79, 1.33)	0.87
Menarche Under 12	173 (17.9)	280 (21.2)	REF	
Menarche 12–14	626 (64.7)	905 (68.5)	1.11 (0.89, 1.38)	0.34
Menarche 15 or older	156 (15.1)	127 (9.6)	**2.00 (1.47, 2.71)**	<0.0001
Exogenous Hormonal Factors				
Ever Use of OCP	629(65.0)	967 (73.2)	**0.61 (0.50, 0.74)**	<0.0001
OCP use by number of years of use:				
No Use	271 (28)	287 (21.7)	REF	
Under 1 year	137 (14.3)	182 (13.9)	0.81 (0.60, 1.08)	0.15
1–5 years	277 (28.8)	385 (29.4)	**0.70 (0.55, 0.90)**	0.005
6–10 years	154 (16.0)	210 (16.0)	**0.71 (0.53, 0.94)**	0.02
More than 10 years	122 (12.7)	246 (18.8)	**0.50 (0.37, 0.66)**	<0.0001
				P for TREND=<0.0001

[a] UCSF, UIC/Duke and MDACC

[b] Adjusted for age (continuous), race and institution

Table 3

Associations in Post-Menopausal Females Between Reproductive Factors or Hormonal Medications and Gliomas: Pooled Data From Three US Studies [a]

Variable	Cases N=549	Controls N=805	OR (95% CI)[b]	p-value
Mean Age (SD)	61.2 (10.6)	61.6 (9.99.0)	**NA**	0.49
	N (%)	N (%)		
Race: White	475 (86.5)	702 (87.2)	**NA**	0.71
Endogenous Hormonal Factors				
Age at menopause 45 or under	210 (37.7)	317 (39.3)	REF	
Age at menopause 46 to 50	166 (30.3)	241 (30.0)	1.04 (0.80, 1.36)	0.75
Age at menopause older than 50	173 (31.6)	247 (30.7)	1.07 (0.83,21.40)	0.62
Exogenous hormonal Factors				
Ever use of OCP	314 (57.2)	532 (66.1)	**0.58 (0.45,0.75)**	<0.0001
OCP use by number of years of use				
OCP no use	184 (33,5)	220 (27.3)	**REF**	
Under 1 year	87 (15.9)	121 (15.0)	**0.91 (0.63, 1.32)**	
1–5 years	137 (25.0)	223 (27.7)	**0.67 (0.49, 0.93)**	
6–10 years	75 (13.7)	103 (12.8)	**0.80 (0.54, 1.19)**	
More than 10 years	61 (11.1)	131 (16.3)	**0.52 (0.35, 0.77)**	
				P for TREND=0.001
Ever use of HRT	271 (49.4)	513 (63.7)	**0.55 (0.44, 0.68)**	<0.0001
HRT use by number of years of use				
HRT no use	225 (41.6)	232 (28.9)	REF	
Under 1 year	76 (14.1)	108 (13.5)	0.83 (0.57, 1.20)	0.32
1–5 years	83 (15.3)	145 (18.1)	**0.60 (0.43, 0.83)**	0.002
6–10 years	51 (9.4)	102 (12.7)	**0.55 (0.37, 0.80)**	0.002
More than 10 years	106 (19.6)	215 (26.8)	**0.53 (0.40, 0.72)**	<0.0001
				P for TREND=<0.0001

[a] UCSF, UIC/Duke and MDACC

[b] Adjusted for age (continuous), race and institution

Table 4

Combined Effects of Lifetime Oral Contraceptive use and HRT use on Glioma Risk in Post-Menopausal Females: Pooled Data From Three US Studies [a]

Variable	Cases N=549	Controls N=805	OR (95% CI)[b]	p-value
OCP and HRT vs neither	164 (29.9%)	346 (43.0%)	**0.34 (0.24, 0.48)**	<0.0001
OCP vs neither	150 (27.3)	186 (23.1)	**0.57 (0.39, 0.81)**	0.002
HRT vs neither	107 (19.5)	167 (20.8)	**0.52 (0.36, 0.74)**	0.0003
Neither OCP nor HRT Use	128 (23.3)	106 (13.2)	**REF**	

[a] UCSF, UIC/Duke and MDACC

[b] Adjusted for age (continuous), race and institution