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Reproductive Factors and Hormone Use and Risk of Adult Gliomas

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Abstract

Previous research suggests there may be a hormonal influence on glioma risk as evidenced by lower rates in females, change in incidence rates around ages at menarche and menopause and presence of hormone receptors in glial tumors. Using the large San Francisco Bay Area Adult Glioma Study, we investigated whether reported reproductive factors and hormone use were associated with gliomas overall or with histologic subtypes among female cases (n=619) and controls (n=650). We found that reproductive factors were generally not associated with gliomas. Weak to moderately elevated odds ratios were observed for self-reported later age at menarche (14+ years old versus 12–13 years old: adjusted odds ratio (AOR) = 1.39, 95% confidence interval (CI): 1.02 –1.89), particularly for non-glioblastoma histologies (AOR = 1.64, 95% CI: 1.11–2.43). Inverse associations were observed for ever self-reported use of exogenous hormones (oral contraceptive use: AOR = 0.72, 95% CI: 0.53–0.99; postmenopausal hormone use: AOR = 0.56, CI: 0.37–0.84). However, cumulative hormone exposure defined multiple ways demonstrated no clear pattern of association. The results of this study suggest that any protective effect of hormones on gliomas may be limited to exogenous hormones, but a more detailed history of exogenous hormone use are needed to confirm findings.

Keywords

reproductive factors; gliomas; case-control study; exogenous hormone use

Introduction

Hormones play a critical role during brain development in-utero;[1,2] appear to work as a neuroprotectant via estrogen-receptor independent pathways in brain degeneration,[3] and may reduce the risk of death and degree of disability in cases of traumatic brain injury.4 Whether similar hormonal pathways are involved in the etiology or progression of brain cancers is unknown, but cell cultures and animal studies demonstrate evidence of estrogen directly killing glioma cells5 and inhibiting the growth of gliomas,6,[7] the most common and deadly brain tumor. Plausible mechanisms by which sex hormones may play a role in gliomagenesis have been postulated. For example, estrogen can inhibit cell cycle entry by increasing mitogen-activated protein kinase (MAPK) levels in astrocytes and stimulating the AKT/PIP pathway to assist in cell cycle control.[8] Other plausible mechanisms include an

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estrogen-astrocyte-TGF-β1 pathway9 and melatonin-driven neuroprotection via aromatase.[10,11]

Data from human studies appear to support a hormonal influence on gliomas, including reports of consistent excess of gliomas among males, hormone receptors in glial tumors, and changes in incidence rates around ages at menarche and menopause. However, epidemiologic studies using reproductive and menstrual history as surrogates of hormone exposure have been generally inconclusive due, in part, to small sample sizes, different histology groupings among glioma classification systems, or the combining of heterogeneous histologic subtypes.[12–22] We used data from the largest population-based case control study of adult brain tumors to date, the San Francisco Bay Area Adult Glioma Study, to estimate the effects of reproductive factors and hormone use on gliomas among women. The large sample size allowed a valuable opportunity for analysis by glial tumor subtype and further exploration of cumulative female hormone using ages at menarche and menopause and years of exogenous hormone use to more completely characterize dose-response relationships and improve on previous studies using reproductive variables indicative of only one point in time.

Materials and Methods

Study participants

Details of subject recruitment and participation rates for the study series 1 and 2 have been described previously[23–25] and protocols for the most recent series 3 were the same as previously used. Briefly, cases diagnosed with histologically confirmed incident gliomas (International Classification of Diseases for Oncology, morphology codes 9380–9481) between August 1991 to April 1994 (Series 1), May 1997 to August 1999 (Series 2), and November 2001 to September 2004 (Series 3) were identified using the Northern California Rapid Case Ascertainment program. Eligible cases had pathologically confirmed glioma, and resided in the 6 county San Francisco Bay Area (Alameda, Contra Costa, Marin, San Mateo, San Francisco, and Santa Clara). Controls were selected from the same residential area as cases were identified using random digit dialing and frequency matched to cases on age (in 5 year age groups), gender, and race/ethnicity (White, Black, Hispanic, Asian, or other).

Of the 1905 eligible cases in the parent study, full interviews were obtained for 1408 cases (74%) and 15 completed an abbreviated questionnaire form (1%). The remaining cases were not included because either they could not speak English (n=24), were too ill (n=1), did not receive physician permission (n=18), did not have sufficient specimen to confirm glioma diagnosis (n=26), were not able to be contacted (n=63), or otherwise refused (n=267). Of the 27,285 phone numbers randomly generated to contact potential controls, 18% never answered the phone after 10 attempts and 13% were business phone numbers. For those phone contacts, nearly 16% refused to give information to assess eligibility and 5% were either too ill or did not understand English. Approximately 7% (n=1908) were eligible controls and 73% (n=1396) agreed to participate and complete the interview. The other eligibles were dropped because either they refused (n=415), did not speak English (n=14), were not located (n=49), or otherwise could not be used (n=43). Eligible cases and controls for this study were restricted to females 20 years and older, leaving 619 cases and 650 controls available for analysis. Among women, the participation rates (defined as number of cases (or controls) consenting to full interview divided by number of eligible cases (or controls)) were 79% for cases and 79% for controls.

Exposure Assessment

Reproductive, menstrual, and exogenous hormone histories were collected via in-person or phone interview with cases (or their proxies) and controls. On average, self-reporting cases were interviewed within 5 months and proxies within 8 months from cases' diagnosis (range: 3 days – 36 months). Proxy respondents were used in 37% of cases and 0.3% of controls. Questions asked included age at first menstrual period, age menstrual periods stopped completely, number of live births, number of pregnancies not surviving to term (question asked only in series 1), age at each birth, oral contraceptive use (ever/never, never/former/current) and duration (years or months), and hormone replacement therapy use (ever/never, never/former/current) and duration (years or months). Menopausal status was determined by whether they were still menstruating (choices included: yes; yes, but pregnant or postpartum; yes, but infrequently, probably perimenopausal; yes, but taking menopausal estrogen now) or were no longer menstruating (choices included no, went through natural menopause; no, had a hysterectomy; no, other). If they reported having a hysterectomy, further inquiry was made into type of surgery (womb removed, womb and both ovaries removed, womb and one ovary removed, one or both ovaries removed, type unknown). Types of surgery were evaluated independently in association with gliomas, but were ultimately combined into a single variable (surgical menopause) due to small numbers in most strata. Women reporting partial hysterectomies (ovaries remained) were categorized as premenopausal if younger than 50 years of age; women reporting a partial hysterectomy at 50 years of age or older or bilateral oopherectomy were categorized as postmenopausal. In the instance where younger women (<45 years of age) reported not having periods due to unknown or sundry reasons (eg. thyroid disorders, polycystic ovarian syndrome), we coded as premenopausal. For analysis of postmenopausal hormone use, we excluded those women with indeterminate menopausal status (n=32 cases and 3 controls). Like previous studies, cumulative hormonal exposure was calculated using combinations of age at menopause, age at menarche, exogenous hormone use, and parity to crudely account for variability of hormone fluctuations throughout reproductive life.[26–28] Other covariates of interest included cigarette smoking, ethnicity, highest degree earned (education), income, and age at diagnosis.

Statistical Analysis

Category boundaries for continuous variables were informed by univariate quartile distributions among controls but cutpoints were primarily determined by known or suspected biological significance provided strata contained more than five persons within each cell. Adjusted odds ratios and 95% confidence intervals were calculated for each reproductive, menstrual, and exogenous hormone factor independently using unconditional logistic regression models. We identified age, ethnicity, and education for potential confounding using causal directed acyclic graphs[29] and further evaluated confounding by stratified analysis and change in the beta coefficient after removal from models (>10% change). Initial models adjusted for ethnicity, education, and age coded using tail-restricted quadratic splines. Menstruation years was additionally adjusted for parity. Since adding study series to the model containing other predictors of glioma did not notably change the odds ratio for all reproductive factors, series was not included in the final model. In addition to analyzing both proxy and self-respondents, we restricted models to self-report females only. Age at diagnosis or interview, menopausal status and smoking were selected a priori as potential effect modifiers for selected reproductive factors and tested using likelihood ratio tests.

Effect measure modification of the ever oral contraceptive use-glioma association by ever postmenopausal hormone use was evaluated by comparing the model with only main effects with the model inclusive of cross-product terms ever oral contraceptive use and ever

postmenopausal hormone use (likelihood ratio test p value < 0.10). Interaction on the additive scale was determined by comparing the observed odds ratio in the doubly exposed (oral contraceptive and postmenopausal hormone use) to the expected OR assuming additive risks.

Continuous variables for main effects were modeled to test for linear trend. Beta coefficients and p value of the Wald test were used to determine if slope differed from zero. Graphical representations using spline regressions were utilized to confirm monotonic trends. Analyses of associations for specific histologic types (grouped as glioblastoma and non-glioblastoma) compared each subtype to the entire control group. All analyses were conducted using SAS 9.1 software (SAS Institute, Inc., Cary, North Carolina).

Results

Baseline characteristics of the 619 cases and 650 controls were similar except that cases were less likely than controls to have a college education (Table 1). The average age at diagnosis was 56.3 (standard deviation = 17.1) and the average age at interview for controls was 55.4 (standard deviation = 16.8). Proxy respondents were much more common for cases (37%) than controls (0.3%) due to cases' death or disability. Of the 229 proxies in this study, most were daughters (32%) and husbands (32%). The average ages at menarche and menopause was 12.6 (standard deviation = 1.7) and 48.8 (standard deviation = 6.3), respectively. Approximately 62% self-reported as postmenopausal, but a lower proportion (52%) was observed when excluding those with indeterminate menopausal status. Postmenopausal women were older in age and less likely to report ever using oral contraceptives (41%) compared to premenopausal women (77%), but were otherwise similar. The majority of tumors among cases were glioblastomas (60%). Missing information with regard to baseline characteristics was minimal and similarly distributed between cases and controls.

Results of multivariable analyses are presented in tables separately for all women and for self-reporting respondents only. We discuss results of self-reporting women only (indicated by odds ratio among index respondents, OR_{index}) since risk estimates were generally not altered by proxy status and self-report is assumed to be more accurate than recall by proxy.

Reproductive factors

After adjusting for age and ethnicity, gliomas were not associated with ever giving birth (OR_{index} = 0.99, 95% CI: 0.73–1.34), or gravidity (OR_{index} = 0.88, 95% CI: 0.46–1.69, Table 2). Categorical odds ratios for increasing age at first birth among parous women were near unity and the slope of the continuous trend estimate for a one-year change in age at first birth was essentially flat ($\beta = -0.03$, 95% CI: −0.03–0.03, p trend = 0.85). Parous women with more children had higher glioma incidence than those with fewer children, with a change in slope per child of $\beta = 0.08$ (95% CI: −0.05–0.21, p trend = 0.23).

Menstrual factors

Using 12–13 year olds as the referent group due to the large proportion of controls with ages at menarche during this period, higher odds ratios were observed for later age at menarche (≥14 years versus 12–13 years old: OR_{index} = 1.39, 95% CI: 1.02–1.89). The odds ratio for later age at menopause (>50 years versus 45–50 years old: OR_{index} = 1.15, 95% CI: 0.74–1.80, Table 2) was consistent with no effect, as was menopausal status (postmenopausal vs. premenopausal: OR_{index} = 1.14, 95% CI: 0.81–1.62, data not shown). Postmenopausal women experiencing a later age at menarche (≥ 14 years) and early onset of menopause (<45 years old) (OR_{index} = 0.87, 95% CI: 0.34–2.20) demonstrated relatively comparable

odds ratios as compared to postmenopausal women with earlier age (<11 years) and average or later age of menopause (OR_{index} = 0.74, 95% CI: 0.23–2.41, data not shown), but effect estimates were imprecise. Further examination of menstruation years adjusted for parity was not informative.

Stratification by histologic tumor type did not alter odds ratios, with the exception of age at menarche (table 3). An odds ratio of 1.64 (95% CI: 1.11–2.43) was calculated for the association between non-glioblastoma cases and later age at menarche (≥14 years) as opposed to glioblastoma cases (OR_{index} = 1.16, 95% CI: 0.77–1.73).

Exogenous hormone use

Odds ratios for the association between exogenous hormone use and gliomas were consistently below 1.0 for all cases and self-reporting cases. An inverse association was observed for ever oral contraceptive use (OR_{index} = 0.72, 95% CI: 0.53–0.99, Table 4). Among ever users, there was no suggestive trend of decreasing odds ratios with longer duration of use, except when restricted to current users of oral contraceptives (β = −0.003 (95% CI: −0.005 – −0.001), p trend = 0.02, data not shown). Likewise, postmenopausal hormone use was inversely associated with gliomas (OR_{index} = 0.56, 95% CI: 0.37–0.85), particularly among those with surgical menopause (OR_{index} = 0.38, 95% CI: 0.13–1.07). The odds ratio for postmenopausal hormone use remained below 1.0 regardless of age at menopause. There was no evidence of linear trend with increasing duration of postmenopausal hormone use among ever users (p trend = 0.84). Among postmenopausal women, previous oral contraceptive use did not modify the inverse association between postmenopausal hormone use and gliomas (table 5). The combined effects of oral contraceptives and postmenopausal hormones were close to expectations for both additive (OR=0.38) and multiplicative (OR=0.46, p value > 0.10) models.

Exploratory analyses by smoking status and age at diagnosis did not uncover effect measure modification.

Discussion

In this large population based case-control study, we generally found no association between reproductive factors and gliomas. Possible exceptions include elevated odds ratios with older age at menarche and protective effects with exogenous hormone use (oral contraceptives and postmenopausal hormonal therapy). Previous studies exploring the relationship between older age at menarche and gliomas found similar results as ours (risk estimates ranged from 1.59 to 2.10).[13,15,18–20] In contrast, we did not observe a difference in risk by menopausal status nor did we find support of a trend with increasing age at menarche as suggested in previous studies.[15,20] Of the few studies stratifying by glioma subtype, ours is the first to demonstrate that older age at menarche is stronger among non-glioblastomas.

Our findings of an inverse association between gliomas and oral contraceptive use and postmenopausal hormone use need to be interpreted cautiously. Given that educational level has been inversely associated with gliomas, the protective effect we observed with use of exogenous hormones may be due to selection bias. If controls of higher education status had been more likely to participate, odds ratios may be overestimated since hormone use is more common among women earning higher education degrees. Nevertheless, our findings agree with most previous case-control studies.[13,15,18,19,21,22] Only one prospective study reported hazard ratios slightly above the null for oral contraceptive use (HR = 1.04, 95% CI: 0.72–1.50),[20] but it is difficult to directly compare their results to those of our case-control because self-reported hormone use was assessed only at baseline. Similar to other studies,

there was generally no suggestive trend of decreasing odds ratios with increasing duration of exogenous hormone use.[15,19–22] To our knowledge, this is the first study to examine potential interaction between oral contraceptives and postmenopausal hormone use. We found no evidence of synergism or antagonism between postmenopausal hormone use and previous oral contraceptive use and gliomas among self-reporting postmenopausal women. Whether these associations are causal or artifactual are unclear since women who use hormonal therapies may be generally healthier.[30–31]

Several studies have investigated the relation between parity and gliomas, but with conflicting results. Four of six studies reported parous women were at reduced risk of gliomas compared with nulliparous women. In the largest population based case control study to date (N=1657 glioma cases), Lambe *et al.* reported a 24% reduced risk in ever parous Swedish women compared to nulliparous women (OR = 0.76 95% CI: 0.66–0.87).12 A more recent but smaller hospital based case control study found similar, but non-significant, results (OR = 0.85 95% CI: 0.54 – 1.35),19 whereas odds ratio for parity were near the null in our study. These findings differ from a population-based study restricted to rural women in the upper Midwestern States (N=341 cases) which reported an elevated odds ratio (OR = 1.22 95% CI: 0.77–1.96) with ever giving birth and gliomas.15 Our results of no association with increasing number of children agree with most, but not all,[12,19] previous studies.

No associations were detected for gravidity, age at first birth, or menopausal status. In addition, there was no clear pattern of association with age at menopause, even when excluding women with indeterminant or unknown menopausal status (that is, including only women reporting natural menopause or bilateral oopherectomy).

Given the evidence from animal studies of the protective effect of estrogen on gliomagenesis and survival, [32–36] the growing literature supporting the role of estrogen (and estrogen metabolites) as a neuro-protectant, particularly in estrogen receptor independent pathways, [37–39] and observations of other female hormones known to restrict angiogenesis in vascular tumors40 like glioblastomas, it is reasonable to expect that greater hormonal exposure would be favorable. Findings from this study do not generally support our hypothesis that greater cumulative exposure to hormones decreases glioma risk. Earlier, rather than later, age at menopause was inversely associated with gliomas, albeit insignificantly. Earlier age at first birth among parous women was near the null and greater menstruation years did not decrease risk in this study of urban women. This is in contrast to findings of decreasing odds ratios with increasing number of menstruation months among rural women.15 Our definition of cumulative exposure (menstruation years) relied on varying definitions, all of which were assessed, but all without information about menstrual regularity. Odds ratios for menstruation years may be overestimated if cases reporting earlier age at menarche and later age at menopause had sporadic menstrual cycles compared to controls. The inconsistency between definitions of cumulative exposure suggests more robust measures are needed to tease out potential differences in effect between exogenous and endogenous hormones.

Although this is one of the largest case-control studies examining reproductive factors and hormonal use in gliomas, there were still important limitations that may affect interpretation of our results. First, delays in interviewing cases may have resulted in a greater amount of exposure misclassification among cases since gliomas can rapidly affect memory and mental functioning. Rapid case ascertainment strategies used in this study likely minimized this potential bias. In addition, non-differential misclassification may have occurred with age at menopause since the menopausal transition makes it difficult to precisely recall age at menopause. Excluding proxies as a strategy to avoid information bias is not optimal since exclusion may create selection bias.41 Second, controls selected using random digit dialing

(RDD) may have created selection bias if responders differed systematically from non-responders.42 Since we do not know more about non-responders, it is difficult to assess the magnitude and direction of this bias. If non-response was driven by telecommunication advances (more cell phone use during series 3 than series 1), we might have expected the odds ratios to differ by series, which we did not. Third, our study lacked detailed information on the hormonal composition of exogenous hormones used and time since last use in order to account for appropriate latency periods. Finally, reproductive factors may be too broad to capture the 'windows' of relevant exposure when one hormone has more impact than another. Exploring such a hypothesis would benefit from the additional consideration of testosterone, for which there is currently no good surrogate. Understanding the independent function of testosterone, estrogen, progesterone in the nervous system is complex due to their apparent dual functions. The same hormone may create a different response in males than females and this difference may vary from one brain region to another 43⁻44 adding to the complexity of which hormone (or more likely which group of hormones) would be largely responsible for lower incidence of gliomas in females.

Strengths of this present study were the relatively large number of histologically confirmed glioma cases and the availability of more detailed information to detect subtle differences in the effect of potential cumulative hormonal exposure. However, we cannot rule out the possibility that the few notable findings were due to other explanations, such as exposure misclassification and unknown or uncontrolled confounders including demographic or social correlates of the reproductive experience.

This study is an important addition to existing literature regarding reproductive factors and gliomas. We provided some of the first results comparing reproductive factors with glioma histologic subtype. Although we observed no overall association with reproductive factors in this study, there was a suggestion of increased risk with older age at menarche, consistent with several previous studies. Our study provided evidence that this positive association is stronger in non-glioblastomas. We acknowledge that non-glioblastomas are still a heterogenous group of tumors, but these results may give insight into differences in risk factors by glioma subtype and impress the need for larger studies (or combining existing studies) in order to garner adequate power for subtype-specific analysis. Furthermore, this study used cumulative exposure as the important next step toward moving beyond assessing reproductive events that are relevant to one point in time. Cumulative exposure, as defined multiple ways in our study, does not appear to be an important in glioma risk, contrary to an observed protective effect among rural women. Given the consistent protective effect with oral contraceptive and postmenopausal hormone use across previous studies, this study was the first to assess whether a potential cumulative or synergistic effect may be relegated to exogenous hormone use only. Future epidemiologic studies could benefit from a more detailed account of exogenous hormone, but without a greater understanding of hormone function in the nervous system interpretation will remain limited. Potentially as informative would be developing a grouping classification system of reproductive factors that could serve as meaningful indices of hormone-specific aggregates to more closely resemble their physiologic function in the body. Future epidemiologic studies could benefit from a more detailed account of exogenous hormone use to confirm findings, but without a greater understanding of hormone function in the nervous system in relation to mechanisms of gliomagenesis interpretation will remain limited. Potentially as informative would be developing a grouping classification system of reproductive factors that could serve as meaningful indices of hormone-specific aggregates (which more closely resembles their physiologic function in the body).

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Abbreviations used are as follows

GBM	glioblastoma
OR	odds ratio

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Table 1

Selected characteristics of glioma cases and controls among female participants in the San Francisco Adult Glioma Study, 1991–2004

	Female participants			
	Case (n=619)		Control (n=650)	
	n	(%)	n	(%)
Age at interview (yrs)				
20–44	173	(28)	192	(30)
45–54	95	(15)	118	(18)
55–64	121	(20)	117	(18)
65+	230	(37)	223	(34)
mean (sd)	56.3 (17.0)		55.4 (16.8)	
Ethnicity				
White	494	(80)	525	(81)
Black	30	(5)	30	(5)
Asian	32	(5)	36	(6)
Hispanic/Mexican	44	(7)	40	(6)
Other	19	(3)	19	(3)
Smoking 100 cigarettes				
Never	325	(53)	332	(51)
Past	225	(36)	234	(36)
Current	66	(11)	83	(13)
Missing	3		1	
Education				
High school or less	301	(49)	259	(40)
College	232	(37)	305	(47)
Graduate school/Professional	85	(14)	86	(13)
Missing	1		0	
Income				
<30,000	153	(25)	194	(30)
30,000–70,000	221	(36)	222	(34)
70,000+	210	(34)	219	(34)
Missing	35	(6)	15	(2)
Marital Status				
Single	75	(12)	91	(14)
Married/spouse	355	(57)	299	(46)
Separated/divorced	85	(14)	145	(22)
Widowed	104	(17)	114	(18)
Missing	0		1	
Histologic Tumor Type				
Glioblastoma	370	(60)		
Astrocytoma	115	(19)		

	Female participants			
	Case (n=619)		Control (n=650)	
	n	(%)	n	(%)
Oligodendroglioma/ Oligoastrocytoma	80	(13)		
Other*	54	(9)		

Numbers do not always total to 100% due to rounding

*other=ependymoma, subependymoma, juvenile pilocytic, astrocytoma- not classified, medulloblastoma, gangliogliomas, and not specified

Table 2

Frequencies and adjusted odds ratios (95% CI) of reproductive factors among glioma cases and controls, and self-reporting participants only in the San Francisco Adult Glioma Study, 1991–2004

Reproductive factors	Cases				Controls (n=650)		OR (95% CI)‡ All women	OR (95% CI)‡ Self-reporting women only
	All women (n=619)		Self-reporting women (n = 390)					
Parity								
Never	139	(22)	116	(30)	164	(25)	1.00 (ref)	1.00 (ref)
Ever	480	(78)	274	(70)	486	(75)	1.08 (0.82–1.44)	0.99 (0.73–1.34)
Missing	0		0		0			
Children								
None	139	(22)	116	(30)	164	(25)	1.00 (ref)	1.00 (ref)
1	100	(16)	59	(15)	128	(20)	0.87 (0.61–1.25)	0.76 (0.51–1.14)
2	188	(30)	116	(30)	181	(28)	1.19 (0.86–1.64)	1.06 (0.74–1.50)
3+	192	(31)	99	(25)	177	(27)	1.15 (0.82–1.63)	1.17 (0.79–1.74)
Gravidity $^{\gamma}$								
Never	38	(19)	27	(26)	37	(18)	1.00 (ref)	1.00 (ref)
Ever	164	(81)	77	(74)	172	(82)	0.85 (0.49–1.48)	0.88 (0.46–1.69)
Missing	1		0		0			
Age at first birth								
Nulliparous	139	(23)	116	(30)	164	(25)	1.00 (ref)	1.00 (ref)
≤20 years old	100	(16)	56	(14)	92	(14)	1.05 (0.73–1.52)	1.05 (0.68–1.60)
21–25 years old	171	(28)	88	(23)	167	(26)	1.09 (0.81–1.45)	1.00 (0.72–1.41)
26–30 years old	128	(21)	80	(21)	141	(22)	1.20 (0.64–2.25)	0.99 (0.47–2.05)
30+ years old	78	(13)	48	(12)	86	(13)	0.89 (0.45–1.75)	0.98 (0.44–2.15)
Missing	3		2		0			
Age at menopause $^{\omega}$								
<45 years old	68	(23)	29	(18)	64	(19)	1.06 (0.67–1.67)	0.87 (0.50–1.54)
45–50 years old	117	(39)	67	(43)	143	(43)	1.00 (ref)	1.00 (ref)
50+ years old	115	(38)	61	(39)	125	(38)	1.22 (0.84–1.75)	1.15 (0.74–1.80)

Reproductive factors	Cases				Controls (n=650)		OR (95% CI)‡ All women	OR (95% CI)‡ Self-reporting women only
	All women (n=619)		Self-reporting women (n = 390)					
Missing	42		2		2			
Menopausal type								
Natural	239	(72)	119	(75)	254	(76)	1.00 (ref)	1.00 (ref)
Surgical	92	(28)	40	(25)	79	(24)	1.00 (0.68–1.46)	1.12 (0.70–1.81)
Don't know	10		0		1			
Missing	1		0		0			
Menstruation years†								
<25 years	133	(26)	120	(31)	166	(26)	1.00 (ref)	1.00 (ref)
25–34 years	179	(35)	136	(35)	209	(32)	1.31 (0.88–1.96)	1.18 (0.76–1.81)
≥35 years	199	(39)	131	(34)	268	(42)	1.29 (0.84–1.99)	1.11 (0.69–1.79)
Missing	108		3		7			

†Menstruation years = menopausal age (or current age, if premenopausal) – menarcheal age; additionally adjusted for parity

‡Adjusted for age (restricted quadratic splines), ethnicity, and education

γobtained in series 1 only

ωamong postmenopausal women

NOTE: Two controls were proxies and were accounted for in the adjusted OR for self-reporting respondents.

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Table 3

Frequencies and adjusted odds ratios (95% CI) of age at menarche and glioma by histologic subtype among all women and among self-reporting women only in the San Francisco Adult Glioma Study, 1991–2004

	Glioblastoma Cases							
	All women (n=370)		**Self-reporting women (n = 180)**		**Controls (n=650)**		**OR (95% CI)‡ All women**	**OR (95% CI)‡ Self-reporting women only**
Age at menarche								
≤11 years old	53	(18)	33	(18)	125	(19)	0.99 (0.68–1.45)	0.95 (0.61–1.50)
12–13 years old	161	(55)	99	(55)	367	(57)	1.00 (ref)	1.00 (ref)
≥14 years old	81	(27)	48	(27)	154	(24)	1.12 (0.80–1.56)	1.16 (0.77–1.73)
Missing	75		0		4			
	Non-glioblastoma Cases							
	All women (n=249)		Self-reporting women (n = 210)		Controls (n=650)		OR (95% CI)‡ All women	OR (95% CI)‡ Self-reporting women only
Age at menarche								
≤11 years old	48	(19)	45	(21)	125	(19)	1.22 (0.81–1.84)	1.28 (0.84–1.96)
12–13 years old	116	(47)	104	(50)	367	(56)	1.00 (ref)	1.00 (ref)
≥14 years old	65	(26)	61	(29)	154	(24)	1.53 (1.05–2.23)	1.64 (1.11–2.43)
Missing	20		0		4			

‡Adjusted for age (restricted quadratic splines),ethnicity, and education

NOTE: Two controls were proxies and were accounted for in the adjusted OR for self-reporting respondents

Table 4

Frequencies and adjusted odds ratios (95% CI) of exogenous hormone use among glioma cases and controls, and self-reporting respondents only in the San Francisco Adult Glioma Study, 1991–2004

	Cases							
Exogenous hormone factors	**All women (n=619)**		**Self-reporting women (n = 390)**		**Controls (n=650)**		**OR (95% CI)‡ All women**	**OR (95% CI)‡ Self-reporting women only**
OC use								
Never	284	(48)	133	(34)	244	(38)	1.00 (ref)	1.00 (ref)
Ever	312	(52)	257	(66)	405	(62)	0.62 (0.47–0.82)	0.72 (0.53–0.99)
Missing	23		0		1			
OC use								
Never	284	(48)	133	(34)	244	(38)	1.00 (ref)	1.00 (ref)
Former	290	(49)	238	(61)	352	(54)	0.65 (0.49–0.86)	0.78 (0.57–1.07)
Current	22	(4)	19	(5)	53	(8)	0.30 (0.16–0.60)	0.26 (0.13–0.53)
Missing	23		0		1			
OC duration								
Never	284	(49)	133	(34)	244	(38)	1.00 (ref)	1.00 (ref)
<1 year	38	(7)	37	(10)	87	(13)	0.35 (0.22–0.54)	0.50 (0.31–0.80)
1–4 years	131	(22)	112	(29)	118	(18)	0.89 (0.63–1.25)	1.08 (0.74–1.57)
5–9 years	67	(12)	56	(15)	86	(13)	0.62 (0.41–0.94)	0.68 (0.44–1.06)
10+ years	62	(11)	48	(12)	114	(18)	0.44 (0.29–0.64)	0.48 (0.31–0.74)
Missing	37		4		1			
PHT use$^{\omega}$								
Never	149	(50)	70	(45)	115	(35)	1.00 (ref)	1.00 (ref)
Ever	149	(50)	84	(55)	214	(65)	0.57 (0.41–0.79)	0.56 (0.37–0.85)
Missing	12		1		2			
PHT use$^{\omega}$								
Never	149	(50)	70	(45)	115	(34)	1.00 (ref)	1.00 (ref)
Former	99	(33)	54	(35)	107	(33)	0.74 (0.51–1.08)	0.78 (0.49–1.23)
Current	50	(17)	30	(19)	107	(33)	0.38 (0.25–0.59)	0.38 (0.22–0.65)
Missing	12		1		2			

Exogenous hormone factors	Cases				Controls (n=650)		OR (95% CI)‡ All women	OR (95% CI)‡ Self-reporting women only
	All women (n=619)		Self-reporting women (n = 390)					
PHT duration$^{\omega}$								
Never	149	(53)	70	(46)	115	(35)	1.00 (ref)	1.00 (ref)
<1 year old	11	(4)	6	(4)	29	(9)	0.27 (0.12–0.57)	0.25 (0.09–0.70)
1–4 years	39	(14)	26	(17)	57	(17)	0.55 (0.33–0.89)	0.57 (0.32–1.03)
5–9 years	23	(8)	15	(10)	31	(9)	0.61 (0.33–1.13)	0.64 (0.31–1.30)
10+ years old	60	(21)	34	(23)	97	(30)	0.51 (0.34–0.77)	0.57 (0.34–0.95)
Missing	28		4		2			

‡adjusted for age (restricted quadratic splines), ethnicity and education

$^{\omega}$among postmenopausal women

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Table 5

Adjusted OR (95% CI) for interaction between oral contraceptive use and postmenopausal hormone use and gliomas among postmenopausal women, and self-reporting respondents only in the San Francisco Adult Glioma Study, 1991–2004

Oral contraceptive use among self-reporting women	**Never postmenopausal hormone use among self-reporting women**		**Ever postmenopausal hormone use among self-reporting women**	
	Case/control	**OR[†] (95% CI)**	**Case/control**	**OR[†] (95% CI)**
Never	38/69	1.00 (ref)	37/108	0.55 (0.30–0.98)
Ever	32/45	0.83 (0.41–1.69)	47/105	0.50 (0.25–0.98)
Oral contraceptive use among all women	Never postmenopausal hormone use among all women		Ever postmenopausal hormone use among all women	
	Case/control	OR[†] (95% CI)	Case/control	OR[†] (95% CI)
Never	102/70	1.00 (ref)	84/108	0.57 (0.37–0.88)
Ever	45/45	0.60 (0.33–1.10)	61/106	0.36 (0.20–0.64)

[†]adjusted for frequency matched factors age (restricted quadratic splines), ethnicity and education