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Reproductive Factors and Risk of Primary Brain Tumors in Women

Gabriella M. Anic[1], **Melissa H. Madden**[1], **L. Burton Nabors**[2], **Jeffrey J. Olson**[3], **Renato V. LaRocca**[4], **Zachary J. Thompson**[5], **Shitaldas J. Pamnani**[1], **Peter A. Forsyth**[6], **Reid C. Thompson**[7], and **Kathleen M. Egan**[1]

[1]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa FL 33612, USA

[2]Neuro-oncology Program, University of Alabama at Birmingham, Birmingham, AL 35294, USA

[3]Department of Neurosurgery, Emory School of Medicine, Atlanta, GA 30322, USA

[4]Norton Cancer Institute, Louisville, KY 40202, USA

[5]Biostatistics and Bioinformatics Department, H. Lee Moffitt Cancer Center & Research Institute, Tampa FL 33612, USA

[6]Department of Neurooncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa FL 33612, USA

[7]Department of Neurological Surgery, Vanderbilt University Medical Center, Nashville, TN 37232, USA

Abstract

Gender-specific incidence patterns and the presence of hormonal receptors on tumor cells suggest that sex hormones may play a role in the pathogenesis of primary brain tumors. However, epidemiological studies on the relation of hormonal risk factors to the risk of brain tumors have been inconsistent. We examined the role of reproductive factors in the onset of glioma and meningioma among women enrolled in a case-control study conducted in the Southeastern US that included 507 glioma cases, 247 meningioma cases, and 695 community-based controls. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) adjusting for age, race, US state of residence, and education. An older age at menarche was associated with an increased risk of glioma (≥15 years versus ≤12 years: OR = 1.65; 95% CI: 1.11, 2.45), with a stronger association observed in pre-menopausal (OR = 2.22; 95% CI: 1.12, 4.39) than post-menopausal (OR = 1.55; 95% CI: 0.93, 2.58) women. When compared to controls, meningioma cases were more likely to have undergone natural menopause (OR = 1.52; 95% CI: 1.04, 2.21) whereas glioma cases were less likely to be long term users of oral contraceptives (OR = 0.47; 95% CI: 0.33, 0.68). Increasing parity was not related to the risk of either tumor. Current findings are consistent with a limited role for hormones in the onset of

*To whom correspondence should be addressed: Kathleen M. Egan, PhD, Department of Cancer Epidemiology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA, kathleen.egan@moffitt.org.

CONFLICT OF INTEREST
The authors have no conflicts of interest to report.

brain tumors in women. Results contribute to a growing body of evidence that a later age at menarche increases the risk of glioma.

Keywords

glioma; meningioma; reproductive factors; exogenous hormones; menarche

INTRODUCTION

Gliomas and meningiomas are the most common types of primary adult brain tumors [1]. Gliomas develop from glial cells (astrocytes or oligodendrocytes) that surround and support neurons in the brain [2]. Although relatively rare, gliomas are one of the most aggressive human tumors with a median survival time of only 12 to 15 months for glioblastomas, the most frequently diagnosed and aggressive type of glioma [3]. Meningiomas are mainly benign tumors derived from meningothelial cells of the arachnoid membrane covering the brain and spinal cord [2]. Although meningiomas are generally slow growing and encapsulated, they can be a source of extensive morbidity.

The etiology of these tumors remains poorly understood; high dose ionizing radiation [4, 5] and genetic susceptibility [6–8] in addition to several rare hereditary disorders [9] remain the only established risk factors but account for a small proportion of cases. The incidence of glioma is approximately 50% higher in men than women [10, 11], with the largest gender differential occurring during women's reproductive years [12]. In contrast, the incidence of meningioma is almost twice as high in women as compared to men [10]. These observations suggest the possibility that sex hormones play a role in the etiology of brain tumors.

In line with a lower incidence of glioma among women, experimental evidence suggests that estrogen exposure may protect against glioma development with estrogen shown to inhibit cell proliferation and to promote apoptosis in glioma cell lines [13–18]. In contrast, estrogen may increase risk of meningioma as suggested by studies demonstrating higher rates of proliferation in meningioma cell lines exposed to estradiol or progesterone [19]. Progesterone, androgen, and estrogen hormone receptors are expressed in both glioma [20–22] and meningioma [23–25] tumors.

Epidemiologic studies examining associations between hormonal and reproductive factors and the risk of brain tumors were conflicting. In line with a possible untoward influence of hormonal exposures in meningioma, female meningioma cases are more likely to report a history of estrogen-related conditions including breast cancer, uterine fibroid tumors, and endometriosis [26–28]. A later age at menarche has consistently been associated with a higher risk of glioma, whereas findings for parity, menopause status, and the use of oral contraceptives have been inconsistent across studies for both brain tumors [29].

Given evidence of a possible role of sex hormones in brain tumor development and conflicting results from previous studies, we examined reproductive factors and oral contraceptive (OC) use as risk factors for glioma and meningioma among females enrolled

in a US case-control study that included 507 glioma cases, 247 meningioma cases, and 695 controls.

METHODS

Study population

Persons aged 18 or older were enrolled in a clinic-based case-control study examining risk factors for primary brain tumors [30]. Brain tumor cases had a recent (within 3 months) diagnosis of primary glioma or meningioma and were identified in neurosurgery and neurooncology clinics in the Southeastern US including Vanderbilt University Medical Center (Nashville, TN); Moffitt Cancer Center (Tampa, FL); University of Alabama at Birmingham (Birmingham, AL); Emory University (Atlanta, GA), and Kentuckiana Cancer Institute (Louisville, KY). Eighty-seven percent of eligible cases were enrolled in the study, a median of 1.0 month following the brain tumor diagnosis (interquartile range: 2 weeks – 1.7 months). Controls included friends and other nonblood-related associates of the cases (n = 141) as well as residents from the same communities as the cases (n = 554), the latter frequency matched on state of residence, age and gender. In the case of the community controls, for each case a commercial survey firm provided a list of ~20 residential phone numbers in the same general neighborhood as the case based on census track and with a presumed household member of the same race, age, and gender as the case. A screening interview was used to confirm presence of an eligible person in the household and to elicit participation. An estimated 50% of contacted eligible households yielded a participating control. Controls reporting a personal history of brain tumor were excluded. The study was approved by Investigational Review Committees at each participating center, and all participants provided written informed consent.

Data collection

Structured interviewer-administered questionnaires were used to collect data on reproductive factors and exogenous hormone use. Participants were asked to report number of pregnancies, total number of children (including live and stillbirths), age at the birth of the first and last child (including live and stillbirths), age at menarche, age at last period, and if menopausal, whether the menopause was due to surgery. Women were also asked if they had used OCs for at least 6 months, total duration of OC use, and whether they were current users.

Statistical analysis

Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between reproductive factors, OC use and brain tumor risk. Age, state, race, and education were adjusted for in multivariable models based on the *a priori* assumption that these factors confounded the association between reproductive factors and brain tumor risk. To test for linear trend, categorical variables were included in the models as ordinal terms. A woman was considered pre-menopausal if she was still menstruating. Women no longer menstruating with an intact uterus and ovaries were classified as having undergone natural menopause. Those with a bilateral oophorectomy and under age 55, the 90th percentile for age at natural menopause among the controls, were

classified as having undergone surgical menopause. Women reporting a hysterectomy without oophorectomy that were younger than age 55 were considered to have an unknown menopausal status, while those older than age 55 were classified as having undergone natural menopause. Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). A p-value <0.05 was considered statistically significant and all statistical tests were two-sided.

RESULTS

The median age at diagnosis for glioma and meningioma cases was 54 and 53, respectively, and the median age of controls at study enrollment was 55 (Table 1). Controls were slightly more likely than either case group to be college educated and the majority of subjects were Caucasian. Glioma cases were comprised of glioblastoma multiforme (GBM) (58%), lower grade astrocytomas (23%), oligodendroglial tumors (15%), and gliomas of other or unspecific histology type (4%).

Table 2 presents results for reproductive factors in relation to the risk of glioma and meningioma. Later age at menarche was associated with a significantly increased risk for glioma (≥15 years versus ≤12 years: OR = 1.65; 95% CI: 1.11, 2.45). When stratifying by menopause status, the association with glioma was stronger among pre-menopausal (OR = 2.22; 95% CI: 1.12, 4.39) than post-menopausal (OR = 1.55; 95% CI: 0.93, 2.58) women (data not shown). Glioma risk was elevated among nulliparous women when compared to women with 2 children (OR = 1.43; 95% CI: 1.00, 2.03), though the trend for increasing parity just missed statistical significance (p for trend = 0.05). There was a suggestion of an inverse association between age at first birth and glioma risk (p for trend = 0.05), although no individual risk estimate was statistically significant. Time since last giving birth and menopausal status were not associated with glioma risk. For meningioma, women undergoing natural menopause had a significant increased risk when compared to pre-menopausal women (OR = 1.52; 95% CI: 1.04, 2.21), with a slight though non-significant excess risk also observed for surgical menopause (OR = 1.21; 95% CI: 0.73, 2.00). Women reporting ever use of OCs had a non-significant decreased risk of glioma (OR = 0.77; 95% CI: 0.57, 1.03). A significant inverse association was restricted to women using OCs for 10 years or longer (OR = 0.47; 95% CI: 0.33, 0.68). Meningioma risk was unrelated to OC use. Other reproductive factors including age at menarche, parity, age at first birth, and years since last giving birth had no association with meningioma risk. Age at menopause and total years of menstruation had no association with the risk of glioma or meningioma (data not shown).

The findings were essentially unchanged when the control group was restricted to community controls. For example, the association between long term OC use (≥10 years) and glioma risk remained significantly inverse after excluding friend controls from the analysis (OR = 0.43; 95% CI: 0.29, 0.62). The results for glioma, including the observed increased risk for older age at menarche and reduced risk with OC use, were similar after restricting the glioma case group to GBMs (Supplemental Table 1). The only difference was that natural menopause, which was not associated with overall glioma risk, was positively associated with risk of GBM (OR = 2.29; 95% CI: 1.57, 3.36).

DISCUSSION

In this case-control study, an increased risk of glioma was observed among women that reported a later age at menarche. Long-term use of OCs (10 or more years) was inversely associated with glioma though not meningioma. Glioma cases were more likely to be nulliparous when compared to controls and menopause was associated with an increased risk for meningioma, although the positive association was only significant for natural menopause. Other factors including increasing parity, age at first birth, and years since last giving birth were not associated with the risk of either type of brain tumor.

An older age at menarche has consistently been associated with an increased glioma risk in epidemiologic studies. In a meta-analysis of six case-control studies, the oldest versus youngest category for age at menarche (variously defined) was associated with a significant 40% excess risk for glioma [31]. Two prospective cohort studies also provide evidence in support of the association. In the study of Kabat et al. based on the NIH-AARP cohort, authors reported a significant positive association with glioma for an age at menarche at 15 years or older versus 12 years or younger adjusting for confounding factors (HR = 1.67; 95% CI: 1.03, 2.69) [32]. In a second prospective analysis based on the Canadian National Breast Screening Study that included almost 90,000 women among whom 120 glioma cases were identified, an older age at menarche was also positively associated with glioma risk though results did not achieve statistical significance (p trend on increasing age at menarche = 0.06) [33]. In both of these studies, no other examined hormonal or reproductive risk factor was associated with glioma risk. Delayed menarche, and therefore fewer menstrual cycles, may be a marker of a lower cumulative estrogen exposure in women, consistent with a beneficial influence of estrogen on glioma risk. On the other hand, menarche is also associated with developmental maturation and the finding may reflect cessation of exposure to growth factors that increase glioma risk. Menarche at a later age has been linked to a taller adult height [34], which is positively associated with insulin-like growth factor 1 (IGF-1) levels during prepubertal growth [35]. Taller adult height has been linked to the risk of glioma in some data [36], although this association was not observed in the present study [30]. The finding for age at menarche was not confounded by adult stature in our study, and the positive association between with increased age at menarche was observed regardless of adult height (Supplemental Table 2) suggesting that the mechanism explaining the finding for age at menarche is not related to exposure to growth factors determining height. In our study, the positive association with later age at menarche was stronger in pre-menopausal women, possibly because younger women more accurately recalled their age at menarche when compared to post-menopausal women with results for the latter group biased to the null. Age at menarche was not associated with the risk of meningioma in the current study; one cohort study of meningioma found a significant increased risk with an older age at menarche [37], however, all other studies observed no association [38–45].

In the present study, women with meningioma were more likely to have undergone menopause, in particular, natural menopause, when compared to controls. The observed excess risk associated with menopause is at variance with the concept that estrogen promotes meningioma given that post-menopausal women have lower cumulative exposure to estrogen as compared to age-similar pre-menopausal women. Post-menopausal status was

associated with an elevated risk of meningioma in some [43, 46], though not all [42, 44, 45] prior case-control studies; whereas cohort studies observed either no association [41] or a significantly lower risk [37] among post-menopausal women. Similar to our finding, most studies [32, 33, 41, 42, 45–49], including three cohort studies [32, 33, 41] observed no association between menopause status and risk of glioma.

Consistent with existing literature our study does not support a role for parity in the onset of brain tumors in women. Although we found a borderline excess risk of glioma in nulliparous women, previous studies have not supported any association of parity with glioma risk [32, 33, 41, 42, 47, 49–52]. Also in line with the present findings, most studies observed no association of parity with risk of meningioma [37, 39–43, 45, 48, 51]. With regard to age at first birth, one case-control study observed a significant inverse association with glioma risk for an early age at first birth compared to nulliparity [45], however consistent with our findings, most studies observed no association between age at first birth and glioma risk [32, 33, 41, 42, 47, 50, 51, 53]. Similarly, no association has been observed between age at first birth and risk of meningioma [37, 38, 40, 41, 43–45, 51, 53]. To the best of our knowledge, no previous studies have reported on associations between years since last giving birth and risk of glioma or meningioma.

In the current study, long-term OC use was associated with a reduction in the risk of glioma but had no association with meningioma. Several case-control studies also observed an inverse association of glioma with ever use of OCs [45, 47, 54]. However, prospective studies have consistently found no association of OC use with glioma risk [32, 33, 41, 51]. Consistent with our finding for meningioma, most studies did not observe an association between OC use and the risk of meningioma [37, 39, 40, 43, 45, 51, 55, 56].

Strengths of this study include pathologic confirmation of all glioma cases and high enrollment rates among the cases. Also, the relatively large number of glioma cases given the rarity of the disease offered substantial power to examine associations of interest. A limitation, however, is the lower than optimal response rate among controls and potential for selection bias in the data. Controls in this study were more educated than either case group and, to the extent that hormone use is more common among women of higher socioeconomic status [57], selection bias may potentially have contributed to the protective association observed for glioma with long term OC use in the current data. While selection bias is difficult to rule out, the null association for OC use in relation to meningioma argues against selective enrollment of OC-using controls, and suggests that the finding for OCs in glioma may potentially have arisen by chance. Another potential source of bias is the use of friend controls since friends are likely to be similar with regard to lifestyle behaviors and socioeconomic status [58]. However, our findings were not materially changed when friend controls were removed from the analysis, suggesting that the inclusion of these controls had no material influence on the results.

In summary, our findings when considered in the context of previous literature offer no consistent evidence for a role of reproductive factors in the onset of brain tumors in women. The study adds to a growing body of evidence that a later age at menarche increases glioma risk, consistent with a potential role for developmental factors in the onset of these tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of female cases and controls.

Variable	Controls (N = 695)	Glioma Cases (N = 507)	Meningioma Cases (N = 247)
Age			
Mean (SD)	54.2 (14.0)	52.6 (15.2)	55.1 (12.8)
Median (range)	55 (19–90)	54 (18–88)	53 (26–87)
Education, N (%)			
High School or Less	202 (29.1)	193 (38.1)	87 (35.2)
Some College	208 (29.9)	142 (28.0)	74 (30.0)
College Degree	180 (25.9)	94 (18.5)	57 (23.1)
Graduate Degree	105 (15.1)	78 (15.4)	29 (11.7)
State of residence, N (%)			
FL	190 (27.3)	177 (34.9)	68 (27.5)
TN	221 (31.8)	113 (22.3)	102 (41.3)
AL	83 (11.9)	100 (19.7)	13 (5.3)
GA	79 (11.4)	53 (10.5)	33 (13.4)
KY	70 (10.1)	37 (7.3)	22 (8.9)
Other	52 (7.5)	27 (5.3)	9 (3.6)
Race, N (%)			
Caucasian	653 (94.0)	478 (94.3)	221 (89.5)
Non-Caucasian	42 (6.0)	29 (5.7)	26 (10.5)
Glioma histology, N (%)			
Glioblastomas		292 (57.6)	
Lower grade astrocytomas		118 (23.3)	
Oligodendroglial tumors		74 (14.6)	
Other gliomas		23 (4.5)	

Table 2

Association between reproductive factors and risk of glioma and meningioma.

				Glioma			Meningioma		
Variable	**Glioma Cases n (%)**	**Meningioma Cases n (%)**	**Controls n (%)**	**Crude OR (95% CI)**	**Multivariable OR (95% CI)[a]**	**p-value**	**Crude OR (95% CI)**	**Multivariable OR (95% CI)[a]**	**p-value**
Age at menarche									
≤12 years	218 (46.7)	113 (46.1)	336 (49.7)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
13 – 14 years	182 (39.0)	101 (41.2)	275 (40.7)	1.02 (0.79, 1.31)	1.07 (0.83, 1.40)	0.60	1.00 (0.74, 1.35)	1.02 (0.75, 1.39)	0.90
≥15 years	67 (14.4)	31 (12.7)	65 (9.6)	1.59 (1.09, 2.33)	1.65 (1.11, 2.45)	0.01	1.33 (0.84, 2.09)	1.37 (0.85, 2.21)	0.20
P_{trend}						0.03			0.32
Parity									
Nulliparous	104 (21.0)	35 (14.2)	110 (16.3)	1.38 (0.99, 1.92)	1.43 (1.00, 2.03)	0.05	0.96 (0.61, 1.51)	0.95 (0.59, 1.53)	0.83
1	89 (17.9)	43 (17.5)	121 (17.9)	1.07 (0.77, 1.50)	1.08 (0.76, 1.53)	0.69	1.07 (0.70, 1.64)	1.05 (0.67, 1.63)	0.84
2	178 (35.9)	86 (35.0)	260 (59.4)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
≥3	125 (25.2)	82 (33.3)	185 (27.4)	0.99 (0.73, 1.33)	0.97 (0.71, 1.34)	0.86	1.34 (0.94, 1.91)	1.25 (0.85, 1.82)	0.26
P_{trend}						0.05			0.31
Age at first birth									
<20 years	93 (18.8)	52 (21.3)	121 (17.9)	1.06 (0.75, 1.48)	1.03 (0.72, 1.47)	0.89	1.10 (0.73, 1.65)	0.95 (0.62, 1.48)	0.83
20–24 years	158 (31.9)	85 (34.8)	217 (32.1)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
25–29 years	94 (19.0)	48 (19.7)	143 (21.1)	0.90 (0.65, 1.26)	0.99 (0.69, 1.41)	0.93	0.86 (0.57, 1.29)	0.84 (0.53, 1.31)	0.43
≥30 years	46 (9.3)	24 (9.8)	85 (12.6)	0.74 (0.49, 1.12)	0.87 (0.55, 1.36)	0.53	0.72 (0.43, 1.21)	0.67 (0.38, 1.19)	0.17
P_{trend}						0.05			0.72
Years since last giving birth									
<10	60 (12.3)	18 (7.8)	85 (12.4)	1.20 (0.76, 1.89)	0.90 (0.53, 1.53)	0.69	0.53 (0.28, 0.98)	0.70 (0.34, 1.43)	0.32
10–19	63 (12.9)	43 (18.6)	107 (15.6)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
≥20	262 (53.6)	135 (58.4)	383 (55.9)	1.16 (0.82, 1.65)	1.27 (0.78, 2.06)	0.33	0.88 (0.59, 1.32)	0.95 (0.54, 1.69)	0.87
P_{trend}						0.12			0.64
Menopause status[b]									
Pre-menopause	157 (31.0)	57 (23.1)	236 (34.0)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
Natural menopause	205 (40.4)	107 (43.3)	289 (41.6)	1.07 (0.81, 1.40)	0.95 (0.72, 1.25)	0.71	1.53 (1.07, 2.21)	1.52 (1.04, 2.21)	0.03
Surgical menopause	63 (12.4)	32 (13.0)	104 (15.0)	0.91 (0.63, 1.32)	0.82 (0.56, 1.20)	0.30	1.27 (0.78, 2.08)	1.21 (0.73, 2.00)	0.46

Variable	Glioma Cases n (%)	Meningioma Cases n (%)	Controls n (%)	Glioma			Meningioma		
				Crude OR (95% CI)	Multivariable OR (95% CI)[a]	p-value	Crude OR (95% CI)	Multivariable OR (95% CI)[a]	p-value
Hormonal contraceptive use for at least 6 months[c]									
Never	133 (27.0)	61 (24.7)	160 (23.6)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
Ever	359 (73.0)	186 (75.3)	519 (76.4)	0.83 (0.64, 1.09)	0.77 (0.57, 1.03)	0.08	0.94 (0.67, 1.32)	1.01 (0.70, 1.48)	0.96
Duration of hormonal contraceptive use[d]									
0 – <1 years	156 (33.0)	72 (29.7)	188 (27.9)	1.00 (Ref)	1.00 (Ref)		1.00 (Ref)	1.00 (Ref)	
1–9 years	224 (47.5)	104 (43.0)	282 (41.8)	0.96 (0.73, 1.26)	0.91 (0.67, 1.24)	0.54	0.99 (0.69, 1.41)	1.12 (0.75, 1.65)	0.58
≥10 years	92 (19.5)	66 (27.3)	205 (30.4)	0.54 (0.39, 0.75)	0.47 (0.33, 0.68)	<0.0001	0.85 (0.58, 1.26)	0.86 (0.56, 1.33)	0.50
P_{trend}						<0.0001			0.46

[a] Multivariable models adjusted for age at diagnosis (3-year categories), state of residence, race (Caucasian/non-Caucasian), and education (high school or less, some college, college graduate, graduate education).

[b] Model does not include age.

[c] Model also adjusted for marital status.

[d] Model also adjusted for number of children (0–1, 2, ≥3).