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Reproductive Factors and Exogenous Hormone Use and Risk of Adult Glioma in Women in the NIH-AARP Diet and Health Study

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Abstract

Experimental evidence suggests that estrogen and other steroid hormones may protect against glioma. Although epidemiologic studies provide only weak support for a role of exogenous or endogenous hormones in gliogenesis, few cohort studies have addressed this question. The authors therefore examined the association between menstrual and reproductive factors, exogenous hormone use, and glioma risk among 225,355 women aged 50 to 71 years who completed the baseline questionnaire in the NIH-AARP Diet and Health Study. During 7 years of follow-up 174 cases of incident, primary glioma were ascertained. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for exposures taking potential confounders into account. 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 results were similar when the analysis was restricted to cases with glioblastoma (N = 130). The present study provides only limited support for the hypothesis that menstrual/reproductive factors or exogenous hormone use play a role in gliogenesis.

Little is known about the etiology of brain cancers, which in general are highly fatal malignancies (1). Glioma is the most common type of brain cancer, representing approximately 80% of cases (2). The only established risk factors for gliomas are high-dose ionizing radiation and certain rare genetic conditions, which together account for only a small proportion of cases (1). Women have a lower incidence rate of gliomas compared to men, and this difference begins to emerge in early adolescence (3, 4), suggesting a possible protective role of female hormones, or, alternatively, a detrimental role of androgens, on the development of glioma. In adulthood, the incidence rate of glioma is 50% greater in men than in women. For example, the age-adjusted annual incidence rate of glioma in the U.S. is 7.6/100,000 in males and 5.4/100,000 in females (2), and the male-to-female excess has been stable over time, a pattern that is evident internationally (5). Additional support for a possible role of steroid hormones in the etiology of glioma comes from the findings that steroid hormone receptors are expressed in normal and malignant glial cells (6–9) and that female athymic mice and nude rats implanted with human glioblastoma cells have been shown to have smaller tumors, a longer latency period, and better survival compared to males (10, 11).

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Epidemiological studies that have examined the association of menstrual/reproductive factors and exogenous hormone use with risk of glioma in women have provided only limited evidence of associations with risk of this malignancy (12–22). However, some studies have had small sample sizes (18, 19) or limited exposure information (14, 19, 20). In several case-control studies, the proportion of proxy respondents for cases was approximately 40% (16, 22). Only three reports are based on cohort studies (14, 18, 20). The most consistent finding to date has been a positive association between a relatively late age at menarche and increased risk of glioma observed in one cohort study (18) and three case-control studies (12, 16, 17). A fourth case-control study (22) noted a positive association of age at menarche with non-glioblastoma but not with glioblastoma.

Given the paucity of prospective data, the authors used data from the NIH-AARP Diet and Health Study to examine associations between reproductive and hormonal factors and the risk of glioma.

Material and Methods

Study population

The NIH-AARP Diet and Health Study is a large prospective cohort study of AARP members initiated in 1995–1996. The rationale and design of the study have been described in detail previously (23). In brief, 617,119 AARP (formerly the American Association of Retired Persons) members between the ages of 50 and 71 years, residing in six U.S. states and two metropolitan areas covered by population-based cancer registries, responded to self-administered questions covering demographic characteristics, dietary intake, and numerous health-related behaviors. The baseline questionnaire was satisfactorily completed by 567,169 of these respondents, of whom 226,733 were women (23). The study was approved by the National Cancer Institute Special Studies Institutional Review Board, and return of the questionnaire signified consent.

Among women with completed questionnaires, we excluded subjects who had questionnaires completed by proxy respondents (N = 1,265), who had prevalent brain cancers (N = 9), who died or moved out of the study area before study entry (N = 63), and who at baseline had brain tumor types which are generally benign or which were ill-defined (N = 41). Our final analytic cohort consisted of 225,355 women.

Information on reproductive history and exogenous hormone use

At baseline, women were asked about their age at first menstrual period; age at first live birth; number of live-born children; age at last menstrual period; whether menopause was natural or due to surgery, radiation, or chemotherapy; history of hysterectomy and oophorectomy; and use of oral contraceptives and hormone therapy. Within 6 months of the baseline questionnaire, respondents were sent a second questionnaire which elicited more detailed information about the type of menopausal hormone therapy (estrogen or progestin), brand, and duration of use. This questionnaire was returned by 134,514 (61%) of the women in our analytic cohort.

Ascertainment of glioma

Histologically confirmed cases of glioma were identified from the eight state population-based cancer registries up to December 31, 2003 (24). A validation study indicated that study procedures identified approximately 90% of all incident cancers within the eight registries (24). The NIH-AARP study obtained all brain tumor reports from the participating registries (ICD-O-2 site: C70.0–C72.9). Because benign brain tumors are not uniformly reported to cancer registries, we excluded a small number of cell types which are mostly

benign (meningiomas – N =12) and uncertain cell types (N = 29) and restricted attention to gliomas (morphology codes: 9380–9481), which are predominantly malignant. Among the 225,355 women, 174 glioma cases were ascertained during a median follow-up period of 7.5 years. One hundred and thirty of these cases had glioblastoma multiforme.

Statistical analysis

Cox proportional hazards models, with person-years as the underlying metric, were used to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for the association of menstrual/reproductive and exogenous hormone use with risk of glioma. Follow-up of the cohort was calculated from the date of receipt of the baseline questionnaire through December 31, 2003 or until death. The analysis was carried out in two stages. First, information from the baseline questionnaire was analyzed for the cohort of 225,355 women among whom 174 cases of glioma were identified. These analyses were repeated for cases of glioblastoma multiforme (N = 130). In the second stage, the more detailed information about menopausal hormone therapy was used. Follow-up for this second analysis was calculated from the date of receipt of the second questionnaire. This analysis was based on 134,514 among whom 106 gliomas cases were identified. Variables were included in the multivariable models if they were associated with glioma risk or if they changed the risk estimate for menstrual/reproductive or hormone use by >10%. The final model included the following variables: age at entry (continuous); race (white/non-white); age at menarche (<13, 13–14, ≥15); parous/nulliparous; age at menopause (<45, 45–49, ≥50), history of hysterectomy (no/yes), and smoking status (never, former, current smoker). In addition, a sensitivity analysis was carried out, excluding glioma cases diagnosed within the first 3 years following baseline. Tests for trend across ordered categorical variables were calculated using the median value for each category.

Results

Risk of glioma was not altered in association with age, education, race, or body mass index (Table 1). Relative to never smokers, the hazard ratio for former smokers was significantly elevated (age-adjusted HR 1.46, 95% CI: 1.05, 2.04), while that for current smokers showed a non-significant increase (age-adjusted HR 1.33, 95% CI: 0.84, 2.12).

Table 2 shows age-adjusted associations between menstrual/reproductive factors, hormone use, and risk of glioma. Older age at menarche showed an increased risk of borderline significance: hazard ratio 1.53 (95% CI: 0.96, 2.44) for age at menarche ≥15 years relative to <13 years. A history of hysterectomy was significantly associated with increased risk of glioma: hazard ratio 1.42 (95% CI: 1.05, 1.92), however a history of oophorectomy was not associated with increased risk. Ever use of oral contraceptives showed a non-significant inverse association with risk; however, there was no trend with increasing duration of oral contraceptive use. Hazard ratios for age at first live birth, parity, type of menopause, age at menopause, ever use of hormone therapy and duration of hormone therapy did not differ from unity.

After adjustment for covariates, the positive associations of older age at menarche with glioma was statistically significant: HR 1.67 (95% CI: 1.03, 2.69). History of hysterectomy, but not of oophorectomy, was associated with increased risk: 1.61, 95% CI: 1.08, 2.40 (Table 3). The associations were of comparable magnitude for glioblastoma but were no longer statistically significant. The reduction in risk in association with ever use of oral contraceptives was unaffected by adjustment for covariates but was not statistically significant (0.76, 95% CI: 0.53, 1.10). The corresponding hazard ratio for glioblastoma was 0.83 (95% CI: 0.55, 1.25). Age at menopause and hormone therapy (current or past use, and duration of use) were not associated with altered risk for all gliomas or for glioblastoma.

When the analysis was repeated excluding glioma cases diagnosed within the first three years of follow-up, the results were unchanged (data not shown).

In the analysis of the more detailed information regarding menopausal hormone therapy available on women who responded to the second questionnaire, the hazard ratios for any hormone use, and ever use of estrogen pills or progestin pills did not differ from unity, and there was no association or trend with duration of estrogen or progestin use (Table 4).

Discussion

Overall, the present study provides little support for a role of menstrual/reproductive factors or hormone use in the etiology of gliomas. Risk of glioma was modestly increased among women with a relatively older age at menarche and among women with a history of hysterectomy, although history of oophorectomy was not associated with increased risk. Similar associations were seen for glioblastoma multiforme, which accounted for 75% of cases. There was a suggestion that ever use of oral contraceptives was associated with reduced glioma risk, but the reduction was not statistically significant, there was no trend with duration of use, and the association was weakened when cases were restricted to glioblastoma. None of the other reproductive or exogenous hormone use examined were related to risk of glioma.

Eleven previous studies (eight case-control [12, 13, 15–17, 19, 21, 22] and three cohort [14, 18, 20]) have examined menstrual/reproductive and/or exogenous hormone use in relation to risk of gliomas. The number of glioma cases ranged from 115 (19) to 1,657 (12). Generally, previous studies have reported weak or null associations with reproductive events. Hatch et al. (16) found that an early age at first birth was associated with reduced risk of glioma, but other studies observed no association (13, 14, 16, 18, 20–22). Two studies (13, 14) reported that parous women were at reduced risk, whereas other studies (15–18, 20–22) observed no effect of parity. Four studies that examined the effect of age at menarche (12, 16–18) reported that women with a relatively older age at menarche were at increased risk. In a large population-based case-control study, Felini et al. (22) observed an increased risk among women with an older age at menarche for non-glioblastoma cases but not for glioblastoma cases. In our study, the association of older age at menarche was unchanged when cases were restricted to glioblastoma multiforme. The large Million Women Study (20) found no associations with age at first birth, parity, or oral contraceptive use, but did not report on associations for age at menarche or postmenopausal hormone use.

Six studies (16–21) have examined exogenous hormone use in relation to risk of glioma. Hatch et al. (17) and Felini et al. (22) found that women who had ever used oral contraceptives were at decreased risk, but there were no clear trends with duration of use, and the remaining studies provided no evidence of an association (16, 18–20). Three studies (16, 17, 22) reported that ever users of hormone therapy had reduced risk of glioma, but there was no trend with duration of use. Two other studies (18, 19) showed no association of ever use of hormone therapy or duration of use with glioma risk. In our study, the first to examine the type of menopausal hormone therapy in relation to risk of glioma, we found no association with ever use of hormone therapy, duration or use, or with ever use or duration of use of estrogen or progestin.

Estrogen is critical in brain development during gestation (25) and prevents loss of nerve cells following injury to the brain (6, 26, 27). However, it is unknown whether estrogen or other hormones play a role in the development of brain cancers. Support for a possible role of hormones in gliogenesis comes from the fact that some glioblastomas express estrogen receptors (6, 28) as well as aromatase, the enzyme responsible for the conversion of

testosterone to estradiol (29). Furthermore, experimental studies have demonstrated that estrogen and 2-methoxyestradiol inhibit proliferation of gliomas (11, 30, 31) and induce cell death (32). The positive association of a relatively older age at menarche with increased risk of glioma seen in a number of studies (12, 16–18, 22), including ours, is consistent with a protective effect of increased exposure to estrogen due to a greater number of menstrual cycles between menarche and menopause. However, other reproductive events which affect exposure to ovarian hormones, and exogenous hormone use did not show a clear association with glioma risk. The weakness of the evidence from epidemiologic studies may reflect the fact that the standard questions on menstrual and reproductive events and hormone use are poor surrogates for actual exposure to circulating hormones, including estrogen, progesterone, prolactin, and testosterone at different points throughout a woman's life.

Strengths of the present study include its prospective design and the extent of information on menstrual/reproductive and exogenous hormone use. However, the number of glioma cases was limited leading to imprecise estimates for some exposures. The number of cases was further reduced in the analysis of subjects who returned the second questionnaire with detailed information on postmenopausal hormone use. In addition, in our study population, only 7 glioma cases occurred among premenopausal women, reflecting the small proportion of premenopausal women in the NIH-AARP study. Also, information on breastfeeding, menstrual cycle pattern, or cumulative number of menstrual cycles over a woman's lifetime was not available. Finally, our analysis was restricted to glioma because other types of brain tumors were not systematically ascertained by the participating registries.

In conclusion, the results of the present study are generally consistent with those of most previous studies and particularly cohort studies in providing little support for a role of menstrual/reproductive factors or exogenous hormone use in the etiology of glioma.

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Table 1

Age-Adjusted Associations of Background Factors With Risk of Glioma Among 225,355 Women in the NIH-AARP Diet and Health Study

	Gliomas (N = 174)	Person-years	HR[a] (95% CI)
Age at enrollment (yrs)			
<60	54	604,515	1.00 (reference)
60–64	52	459,817	1.06 (0.56, 2.00)
≥65	68	565,185	0.98 (0.37, 2.62)
Education			
High school or less	61	512,776	1.00 (reference)
Post high school	16	172,210	0.80 (0.46, 1.38)
Some college	45	402,718	0.97 (0.66, 1.42)
College grad or post-college	51	486,719	0.92 (0.63, 1.33)
Missing	1		
Race			
Caucasian	160	1,456,388	1.00 (reference)
Other/unknown	14	173,128	0.75 (0.43, 1.29)
Smoking			
Never	62	717,301	1.00 (reference)
Former	79	628,410	1.46 (1.05, 2.04)
Current	25	225,724	1.33 (0.84, 2.12)
Missing	8		
Body mass index (kg/m^2)			
<25	77	698,397	1.00 (reference)
25–29	52	512,525	0.90 (0.64, 1.28)
≥30	38	366,733	0.94 (0.64, 1.38)
Missing	7	51,860	

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Adjusted for age at entry as a continuous variable.

Table 2

Age-Adjusted Associations of Reproductive Factors and Hormone Use With Risk of Glioma Among 225,355 Women in the NIH-AARP Diet and Health Study

	Gliomas (N = 174)	Person-years	HR[a] (95% CI)
Age at menarche (yrs)			
<13	77	790,914	1.00 (reference)
13–14	70	669,902	1.06 (0.74, 1.46)
≥15	23	151,592	1.53 (0.96, 2.44)
Missing	4	17,108	
P for trend			*0.16*
Age at first live birth (yrs)			
Nulliparous	28	235,516	1.00 (reference)
<20	32	284,450	0.95 (0.57, 1.58)
20–24	68	699,601	0.79 (0.51, 1.23)
≥30	41	383,175	0.87 (0.54, 1.40)
Missing	5	26,775	
Parous/nulliparous			
Nulliparous	30	248,161	1.00 (reference)
Parous	140	1,363,196	0.83 (0.56, 1.23)
Missing	4	18,159	
Parity			
Nulliparous	30	248,161	1.00 (reference)
1	19	169,685	0.93 (0.52, 1.65)
2	41	422,117	0.80 (0.50, 1.28)
≥3	80	771,394	0.83 (0.54, 1.26)
Missing	4	2,548	
History of hysterectomy			
No	81	919,284	1.00 (reference)
Yes	87	687,972	1.42 (1.05, 1.92)
Missing	6	22,259	
History of oophorectomy			
No	109	1,117,365	1.00 (reference)
Both ovaries removed	48	376,483	1.01 (0.58, 1.76)
Other surgery	12	103,557	0.78 (0.47, 1.31)
Missing	5	32,112	
Menopausal status			
Premenopausal	7	70,842	1.14 (0.52, 2.49)
Postmenopausal	164	1,537,075	1.00 (reference)
Missing	3	21,600	
Type of menopause[b]			
Natural	87	880,004	1.00 (reference)
Surgery/radiation/chemo	77	643,657	1.23 (0.90, 1.67)

	Gliomas (N = 174)	Person-years	HR[a] (95% CI)
Missing	6	66,956	
Age at menopause[b]			
≥50	56	608,858	1.00 (reference)
45–49	43	386,466	1.17 (0.80, 1.72)
<45	65	541,751	1.27 (0.91–1.79)
Missing	3	21,500	
Oral contraceptive use			
Never	117	970,560	1.00 (reference)
Ever	53	633,935	0.74 (0.53, 1.05)
Missing	4	25,021	
Duration of OC use			
Never	117	970,560	1.00 (reference)
1–4 yrs	23	282,728	0.73 (0.46, 1.15)
5–9 yrs	17	198,153	0.77 (0.45, 1.29)
≥10 yrs	13	153,054	0.75 (0.42, 1.34)
Missing	4	25,021	
P for trend			*0.22*
Hormone therapy			
Never	87	770,682	1.00 (reference)
Ever	87	858,834	0.94 (0.72, 1.23)
Hormone therapy			
Never	87	770,682	1.00 (reference)
Former	17	161,149	1.16 (0.75, 1.78)
Current	70	695,008	1.05 (0.94, 1.18)
Duration of hormone use			
Never	80	728,152	1.00 (reference)
<5 yrs	33	312,649	1.17 (0.82, 1.67)
5–9 yrs	22	214,010	0.91 (0.58, 1.41)
≥10 yrs	32	329,564	0.83 (0.57, 1.20)
Missing	7	6,318	
P for trend			*0.23*

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Adjusted for age at entry as a continuous variable.

[b]Restricted to postmenopausal women.

Missing values: age at menarche (4 cases/2397 non-cases); age at first live birth (5 cases/3738 non-cases); parity (4 cases/2544 non-cases); hysterectomy status (6 cases/3120 non-cases); oophorectomy status (5 cases/4494 non-cases); menopausal status (3/3012), age at menopause (3 cases/3012 non-cases); oral contraceptive use (4 cases/3499 non-cases); duration of oral contraceptive use (4 cases/3499 non-cases); ever hormone use (0 cases/0 non-cases); hormone status (0 cases/374 non-cases); years of hormone therapy (7 cases/6311 non-cases).

Table 3

Multivariable-Adjusted Associations of Reproductive Factors and Hormone Use With Risk of Glioma Among 225,355 Women in the NIH-AARP Diet and Health Study

	Gliomas (N=174)	HR[a] (95% CI)	Glioblastomas (N=130)	HR[a] (95% CI)
Age at menarche (yrs)				
<13	77	1.00 (reference)	59	1.00 (reference)
13–14	70	1.01 (0.71, 1.42)	52	0.93 (0.63, 1.38)
≥15	23	1.67 (1.03, 2.69)	17	1.63 (0.95, 2.81)
Missing	4		2	
P for trend		*0.15*		*0.32*
History of hysterectomy				
No	81	1.00 (reference)	59	1.00 (reference)
Yes	87	1.61 (1.08, 2.40)	68	1.52 (0.96, 2.39)
Missing	6		3	
Age at menopause[b]				
≥50	56	1.00 (reference)	39	1.00 (reference)
45–49	43	1.18 (0.80–1.74)	35	1.28 (0.81–2.04
<45	65	1.30 (0.92–1.85)	51	1.11 (0.68–1.81)
Missing	3		1	
Oral contraceptive use				
Never	117	1.00 (reference)	87	1.00 (reference)
Ever	53	0.76 (0.53, 1.10)	41	0.83 (0.55, 1.25)
Missing	4		2	
Hormone therapy				
Never	87	1.00 (reference)	61	1.00 (reference)
Former	17	0.86 (0.50, 1.49)	14	1.00 (0.66, 1.52)
Current	70	0.81 (0.56, 1.18)	55	1.01 (0.54, 1.88)
Missing	0		0	
Duration of hormone use				
Never	80	1.00 (reference)	58	1.00 (reference)
≤5 yrs	33	1.03 (0.67, 1.60)	28	1.29 (0.79, 2.10)
5–9 yrs	22	0.84 (0.49, 1.44)	14	0.87 (0.46, 1.65)
≥10 yrs	32	0.70 (0.44, 1.12)	27	0.85 (0.50, 1.43)
Missing	7		3	
P for trend		*0.11*		*0.35*

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Each variable in the table is adjusted for the remaining variables: age at entry (continuous), race (white/non-white), age at menarche (<13, 13–14, ≥15), parous/nulliparous, age at menopause (<45, 45–49, ≥50), history of hysterectomy (yes/no), and smoking status (never, former, current smoker).

[b]Postmenopausal women only.

Table 4

Association of Type of Exogenous Menopausal Hormone Use with Risk of Glioma Among 134,514 Women in the NIH-AARP Diet and Health Study

	Cases (N = 106)	Person-years	HR[a] (95% CI)
Any menopausal hormone			
Never	38	377,352	1.00 (reference)
Ever	61	582,311	0.99 (0.63, 1.56)
Estrogen pills			
Never	39	386,862	1.00 (reference)
Ever	57	542,592	0.97 (0.61, 1.54)
Duration of estrogen pill use			
Never	38	383,790	1.00 (reference)
1–9 yrs	34	293,431	1.31 (0.79, 2.17)
≥10 yrs	23	241,723	0.69 (0.38, 1.28)
Progestin pills			
Never	65	650,772	1.00 (reference)
Ever	30	277,596	1.24 (0.75, 2.05)
Duration of progestin pill use			
Never	61	641,280	1.00 (reference)
1–9 yrs	22	205,138	1.39 (0.80, 2.42)
≥10 yrs	8	64,770	1.02 (0.40, 2.59)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]Each variable in the table is adjusted for: age at entry (continuous), race (white/non-white), age at menarche (<13, 13–14, ≥15), parous/nulliparous, age at menopause (<45, 45–49, ≥50), history of hysterectomy (yes/no), and smoking status (never, former, current smoker).