Association between hormone therapy and glioma risk in US women: a cancer screening trial

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Abstract

Objective: Gliomas are the most common primary brain tumors in adults, and the role of hormone therapy (HT) in their development remains controversial. This study with a cohort design aimed to investigate the association between HT use and glioma risk using the data from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial.

Methods: We analyzed data from 75,335 women, aged 50-78, who were enrolled between 1993 and 2001. The median follow-up period was 11.82 years. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationship between HT use and glioma risk, adjusting for various potential confounders.

Results: Over the follow-up period, 101 participants were diagnosed with glioma. After adjusting for relevant variables, there was no significant association between HT use and glioma risk (HR, 1.16; 95% CI, 0.75-1.81). Similarly, no significant associations were found when considering HT status or duration of use. However, in subgroup analysis by education, marital status, body mass index, oral contraceptive, hysterectomy, ovariectomy, ever been pregnant, age at menarche, and age at menopause, we found that a significant positive association was only observed in the group with at least college graduate (HR, 3.00; 95% CI, 1.02-8.84). The interaction effect for education was not significant ($P = 0.056$)

Conclusions: Our findings suggest no overall link between HT use and glioma risk. Further research is needed to confirm these results.

Key Words: Cohort, Glioma, Hormone, Hormone therapy, Risk.

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The incidence of glioma, a common brain malignancy with limited effective treatments, consistently exhibits a gender disparity.[1] In particular, in the case of glioblastoma, which is the most aggressive and frequent subtype, accounting for 61.9% of adult gliomas,[2] the male-to-female incidence ratio reaches as high as 1.6.[1] To date, the underlying cause of this sex-related difference remains unknown, as ionizing radiation is the only well-established environment risk factor for glioma, yet its rare occurrence explains only a small fraction of cases.[3] In addition to common risk factors, such as variations in lifestyle, there has been speculation regarding the potential contribution of both exogenous and endogenous sex hormones to glioma development.[4-18]

Hormone therapy (HT) is frequently prescribed to alleviate vasomotor symptoms and genitourinary syndrome, including hot flashes, night sweats, mood swings, vulvovaginal atrophy, and incontinence, in postmenopausal women and younger individuals experiencing early menopause due to surgical intervention, chemotherapy, or radiotherapy.[19,20] The widespread use of HT is evident, with an estimated 600 million woman-years of HT usage recorded in Western countries over the past 50 years, beginning in 1970.[19,21,22] As a result, a thorough understanding of the therapeutic benefits of HT in comparison to its potential risks is crucial for optimizing clinical decision-making and enhancing women's health outcomes. Epidemiological studies have yielded inconsistent findings concerning the relationship between HT and glioma risk, as highlighted in two meta-analyses published in 2018[23] and 2023.[24] In their analysis, both of them observed a significant protective effect of HT in case-control studies, not in cohort studies.[23,24] Importantly, retrospective case-control studies were always subject to selection and recall bias, and a small number of prospective cohort studies included a limited number of cases due to the rarity of glioma. Therefore, additional prospective evidence is necessary to improve the validity of these findings. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial prospectively collected a wide range of personal exposure information and health outcomes.[25] In this study, we employed a cohort design using data from PLCO Trial to explore the association between HT use and glioma risk in women.

METHODS

Data sources and study design

The PLCO is a large-scale population screening trial, which recruited approximately 155,000 participants between the ages of 42 and 78 over the years 1993 to 2001 and was specifically designed to assess the efficacy of screening procedures in reducing mortality from PLCO-related cancers at 10 centers across the United States. Informed consent was obtained from all participants involved in the PLCO study. The comprehensive methodology for this trial has been thoroughly outlined in previous publications.[25-27] Our research, utilizing

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Ethical approval: Our research, utilizing data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, was conducted under an approved National Cancer Institute (NCI) protocol (PLCO-712).

Availability of data and materials: The data of the current study are available from the NIH PLCO study group subject to restrictions, as the data were used under license for the current study. Any requests to access the datasets should be directed to https://cdas.cancer.gov/plco/.

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PLCO data, was conducted under an approved National Cancer Institute protocol (PLCO-712) and follows the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[28]

Data collection

The Baseline Questionnaire (BQ), serving as the initial risk factor assessment, collects self-reported data from participants. This includes details such as basic demographics, smoking history, family cancer history, height, weight, and body mass index (BMI), as well as medical conditions and disease history. Additionally, it gathers personal cancer history along with gender-specific information. For female participants, questions primarily focused on exogenous hormone usage and reproductive or menstrual factors, whereas male participants were inquired about prostate-related conditions or treatments.

Exposure data

Data about HT use was collected from the BQ female-specific questions: "Question F51-Sometimes women take female hormones such as estrogen or progesterone around the time of menopause. Have you ever used female hormones (tablets, pills, or creams) for menopause?" "Question F52-Are you currently using female hormones?" "Question F53-how many total years did you take female hormones?" The specific estrogen or progesterone exposure was not addressed in the BQ.

Follow-up and case ascertainment

Cancer reports were gathered through multiple sources, including self-reports, reports from family members, and death certificates. The Annual Study Update inquired about cancer diagnoses with the question: "Have you been diagnosed with cancer by a healthcare provider?" Upon reporting a cancer diagnosis, participants were asked to provide additional details, such as the diagnosis date, cancer type, the hospital or clinic involved, and the contact information (name, phone number, and address) of the diagnosing physician. All cancer reports were followed up, and relevant medical records were retrieved. To identify site-specific cancers, the International Classification of Diseases for Oncology, Second Edition, was employed.

The follow-up period began on the date when the participant was randomized and had completed the BQ. The follow-up concluded on the earliest occurrence of one of the following events: glioma diagnosis, death, trial withdrawal, or the censoring date of the PLCO study, which was December 31, 2009.

Participant selection

The BQ form was distributed to all participants, with a completion and collection rate of 96.8%. According to the PLCO criteria for glioma eligibility, participants qualified if they had completed the BQ, had no prior history of glioma cancer before BQ entry, and had available follow-up data post-BQ. In this study, we focused on evaluating the association between HT and glioma risk in females. As a result, females lacking HT exposure data and males were excluded from the analysis. Additionally, cases involving malignant central nervous system tumors of unknown or other types were also removed. The workflow for participant selection is illustrated in Figure 1.

Statistical analysis

All data were processed using R software version 3.4.3 (http://www.R-project.org) and EmpowerStats version 2.0 (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). The proportionality of hazards was evaluated through the Schoenfeld residuals method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived using Cox proportional hazards regression, with follow-up time serving as the time metric. Model 1 was unadjusted, containing no covariates. In the present investigation with 75,335 women, the racial composition was as follows: 66,777 identified as White, non-Hispanic; 4,270 as Black, non-Hispanic; 1,195 as Hispanic; 2,508 as Asian; 358 as Pacific Islander; 201 as American Indian; and 26 were classified as unknown. Therefore, race was categorized into two groups: "White, non-Hispanic" and "others." Model 2 was adjusted for a range of variables, including age (continuous), race (White, non-Hispanic, others), education (up to high school, post high school or some college, at least college graduate), marital status (ever married or living as married, widowed/divorced/separated, never married), body mass index (BMI: <25, 25-30, ≥30 kg/m^2), personal history of cancer (excluding glioma) (yes, no), cigarette smoking

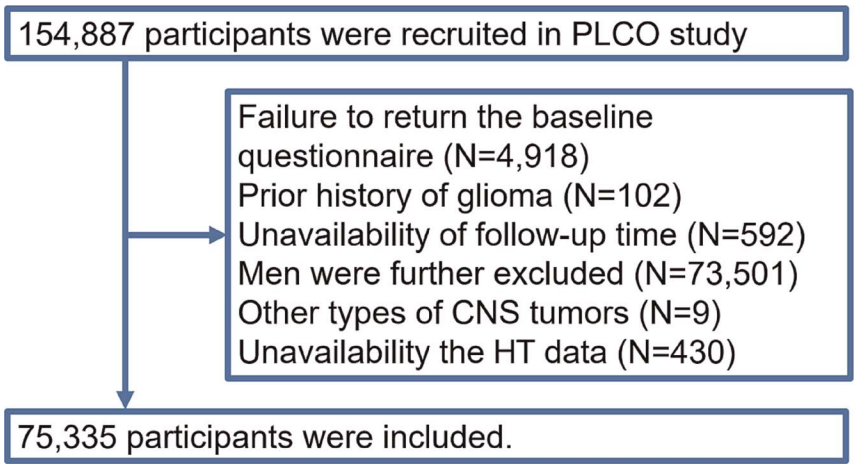

FIG. 1. Flow chart. CNS, central nervous system; HT, hormone therapy; PLCO, Prostate, Lung, Colorectal and Ovarian.

history (never smoking, ever smoking), hysterectomy (no, yes), oophorectomy (no, partial, one ovary-total, both ovaries-total), oral contraceptive (OC) use (never, ever), ever been pregnant (never, ever), age at menarche (≤11, 12-13, ≥14 y), and age at menopause (<44, 45-49, ≥50 y). The selection of these covariates was informed by clinical expertise and a comprehensive review of pertinent prior research. In this study, data on age and race were complete. For the remaining covariates, which were categorical variables with fewer than 5% of data missing, mode imputation was applied to address missing values.[29] Sensitivity

TABLE 1. Baseline characteristics

Variables	All cohort	Non-HT users	HT users
Sample size	75,335	25,316	50,019
Age (y), median (Q1, Q3)	62.0 (58.0, 67.0)	64.0 (59.0, 68.0)	61.0 (57.0, 66.0)
Arm, n (%)			
Intervention	37,779 (50.1)	12,622 (49.9)	25,157 (50.3)
Control	37,556 (49.9)	12,694 (50.1)	24,862 (49.7)
Race, n (%)			
White, non-Hispanic	66,777 (88.6)	21,730 (85.8)	45,047 (90.1)
Others	8,558 (11.4)	3,586 (14.2)	4,972 (9.9)
Education, n (%)			
Up to high school	25,766 (34.2)	10,533 (41.6)	15,233 (30.5)
Some college	27,152 (36.0)	8,616 (34)	18,536 (37.1)
At least college graduate	22,417 (29.8)	6,167 (24.4)	16,250 (32.5)
Marital status, n (%)			
Married or living as married	51,973 (69.0)	16,220 (64.1)	35,753 (71.5)
Widowed/divorced/separated	20,819 (27.6)	7,969 (31.5)	12,850 (25.7)
Never married	2,543 (3.4)	1,127 (4.4)	1,416 (2.8)
Personal history of cancer (except glioma), n (%)			
No	70,234 (93.2)	23,072 (91.1)	47,162 (94.3)
Yes	5,101 (6.8)	2,244 (8.9)	2,857 (5.7)
Body mass index (kg/m^2), n (%)			
<25	31,683 (42.1)	9,467 (37.4)	22,216 (44.4)
≥25,<30	25,537 (33.9)	8,535 (33.7)	17,002 (34)
≥30	18,115 (24.0)	7,314 (28.9)	10,801 (21.6)
Cigarette smoking history, n (%)			
Never smoking	41,926 (55.7)	14,555 (57.5)	27,371 (54.7)
Ever smoking	33,409 (44.3)	10,761 (42.5)	22,648 (45.3)
Hysterectomy, n (%)			
No	47,987 (63.7)	19,841 (78.4)	28,146 (56.3)
Yes	27,348 (36.3)	5,475 (21.6)	21,873 (43.7)
Ovariectomy, n (%)			
Not removed	60,123 (79.8)	22,582 (89.2)	37,541 (75.0)
Partial	1,438 (1.9)	426 (1.7)	1,012 (2)
One ovary-total	4,185 (5.6)	1,198 (4.7)	2,987 (6)
Both ovaries-total	9,589 (12.7)	1,110 (4.4)	8,479 (17)
Oral contraceptives, n (%)			
Never use	34,427 (45.7)	14,366 (56.7)	20,061 (40.1)
Ever use	40,908 (54.3)	10,950 (43.3)	29,958 (59.9)
Ever been pregnant, n (%)			
Never	5,636 (7.5)	2,075 (8.2)	3,561 (7.1)
Ever	69,699 (92.5)	23,241 (91.8)	46,458 (92.9)
Age at menarche, n (%)			
≤11	15,308 (20.3)	5,080 (20.1)	10,228 (20.4)
12–13	40,554 (53.8)	13,437 (53.1)	27,117 (54.2)
≥14	19,473 (25.8)	6,799 (26.9)	12,674 (25.3)
Age at menopause, n (%)			
≤44	21,362 (28.4)	5,747 (22.7)	15,615 (31.2)
45–49	17,822 (23.7)	6,425 (25.4)	11,397 (22.8)
≥50	36,151 (48.0)	13,144 (51.9)	23,007 (46)

HT, hormone therapy; n, number, y, year.

analyses were also performed, during which a repeated analysis was carried out without the imputation of missing data. This approach aimed to assess whether the imputation process had any influence on the final outcomes.

This study initially examined the relationship by comparing ever users with never users. To evaluate the impact of HT use status on glioma risk, HT use was divided into three groups: never use, current use, and former use. Considering that social determinants such as marital status and educational level may impact the decision to use HT, we conducted a subgroup analysis based on these variables. Furthermore, to investigate whether HT is associated with an increased risk of glioma in women with elevated levels of both endogenous and exogenous estrogen exposure, an additional subgroup analysis was undertaken, factoring in variables such as BMI, OC, history of hysterectomy or oophorectomy, ever been pregnant, age at menarche, and age at menopause within the current studies. Potential interactions across these subgroups were evaluated using the likelihood ratio test. The Bonferroni correction was utilized to adjust the *P* value for multiple comparisons across subgroup factors, calculated as 0.05 divided by n (n = 9). Lastly, the study also investigated the association between the duration of HT use and glioma risk, categorizing the duration into four groups: 0, ≤5, 6-9, and ≥10 years.

AI statement

In this study, we used AI tools to improve the spelling, grammar, clarity, conciseness and overall readability of the text.

RESULTS

Following the application of exclusion criteria, the study cohort was reduced to 75,335 women, with a median age of 62 years. During a median follow-up period of approximately 11.82 years, 101 cases of glioma were identified. The majority of the participants (88.6%) were White and non-Hispanic, with 69% either married or cohabitating. Among those utilizing HT, participants were more frequently characterized by having education levels beyond post high school, undergoing hysterectomy and/or ovariectomy, being users of OC, and experiencing a later onset of menopause (see Table 1).

Initially, a comparative analysis was conducted between HT users and nonusers. In the unadjusted model, no significant association between HT use and glioma risk was identified (HR, 1.04; 95% CI, 0.69-1.58). After adjusting for covariates, the findings remained nonsignificant (HR, 1.16; 95% CI, 0.75-1.81). Additionally, when accounting for HT status, neither current nor former users exhibited any significant differences in glioma risk compared to those who had never used HT (Table 2). Further subgroup analyses based on marital status, educational level, BMI, OC use, hysterectomy, oophorectomy, ever been pregnant, age at menarche, and age at natural menopause indicated a significant positive association was only identified among individuals with at least a college degree (HR, 3.0; 95% CI, 1.02-8.84, Table 3). Interaction effect analysis showed that there may be an interaction between ovariectomy and HT on the glioma risk (*P* for interaction = 0.028). However, after applying Bonferroni correction for multiple comparisons, the interaction effect was not significant for ovariectomy and HT ($P > 0.0056$). The analysis examining the duration of HT use similarly revealed no significant associations (Table 2). Specifically, the HRs were 1.33 (95% CI, 0.82-2.17) for those using HT for less than 5 years, 0.47 (95% CI, 0.18-1.23) for 6-9 years of use, and 1.23 (95% CI, 0.70-2.16) for more than 10 years of HT use.

In the sensitivity analyses, a repeated evaluation was conducted without imputing missing data to assess whether the imputation of missing data had any impact on the results. The final cohort comprised 72,052 participants regarding HT use. The HRs were 1.19 (95% CI, 0.76-1.88) for individuals who had ever used HT, 1.30 (0.80-2.12) for current users, and 1.00 (95% CI, 0.53-1.85) for former users. Similar findings were observed when examining the duration of HT use. The HRs and corresponding 95% CIs were 1.36 (0.83-2.24) for

TABLE 2. HT and glioma risk

Variable	Cohort	Cases	Model 1 HR (95% CI)	*P*	Mode 2 HR (95% CI)	*P*
HT						
Never use	25,316	33	1 (Ref.)		1 (Ref.)	
Ever use	50,019	68	1.04 (0.69-1.58)	0.843	1.16 (0.75-1.81)	0.511
HT status						
Never use	25,316	33	1 (Ref.)		1 (Ref.)	
Current use	37,126	53	1.10 (0.71-1.69)	0.677	1.28 (0.80-2.06)	0.309
Former use	12,792	15	0.90 (0.49-1.65)	0.723	0.94 (0.51-1.74)	0.841
Years of HT use						
Never use	25,183	33	1 (Ref.)		1 (Ref.)	
≤5	22,693	36	1.20 (0.75-1.93)	0.447	1.33 (0.82-2.17)	0.248
6-9	9,095	5	0.42 (0.16-1.07)	0.068	0.47 (0.18-1.23)	0.122
≥10	18,144	27	1.15 (0.69-1.92)	0.585	1.23 (0.70-2.16)	0.462

CI, confidence interval; HR, hazard ratio; HT, hormone therapy; Ref., reference.

Model 1 was not adjusted for any covariates.

Model 2 was adjusted for age (continuous), race, marital, education, body mass index, cigarette smoking history, personal history of cancer (except glioma), oral contraceptive use, hysterectomy, ovariectomy, ever been pregnant, age at menarche, and age at menopause.

TABLE 3. Subgroup analysis of HT (ever versus never) and glioma risk

Subgroup	HT use	Cohorts	Cases	Model 2 HR (95% CI)	*P* for interaction
Education					0.056
Up to high school	Never	10,533	16	1 (Ref.)	
	Ever	15,233	19	1.00 (0.50-2.03)	
Post high school or some college	Never	8,616	13	1 (Ref.)	
	Ever	18,536	21	0.77 (0.37-1.61)	
At least college graduate	Never	6,167	4	1 (Ref.)	
	Ever	16,250	28	3.00 (1.02-8.84)	
Marital status					0.991
Married or living as married	Never	16,220	21	1 (Ref.)	
	Ever	35,753	49	1.20 (0.70-2.06)	
Widowed/divorced/separated	Never	7,969	9	1 (Ref.)	
	Ever	12,850	15	1.19 (0.50-2.87)	
Never married	Never	1,127	3	1 (Ref.)	
	Ever	1,416	4	0.84 (0.15-4.77)	
Body mass index, kg/m^2					0.435
<25	Never	9,467	10	1 (Ref.)	
	Ever	22,216	34	1.62 (0.78-3.39)	
≥25, and <30	Never	8,535	14	1 (Ref.)	
	Ever	17,002	22	0.98 (0.48-2.01)	
≥30	Never	7,314	9	1 (Ref.)	
	Ever	10,801	12	0.88 (0.34-2.22)	
Oral contraceptive					0.515
Never use	Never	14,366	24	1 (Ref.)	
	Ever	20,061	34	0.89 (0.51-1.56)	
Ever use	Never	10,950	9	1 (Ref.)	
	Ever	29,958	34	1.71 (0.8-3.66)	
Hysterectomy					
No	Never	19,841	25	1 (Ref.)	0.475
	Ever	28,146	41	1.3 (0.78-2.19)	
Yes	Never	5,475	8	1 (Ref.)	
	Ever	21,873	27	0.87 (0.38-1.97)	
Ovariectomy					0.028
Not removed	Never	22,582	28	1 (Ref)	
	Ever	37,541	56	1.29 (0.80-2.07)	
Partial	Never	426	2	1 (Ref.)	
	Ever	1,012	0	NA	
One ovary-total	Never	1,198	0	1 (Ref.)	
	Ever	2,987	3	NA	
Both ovaries-total	Never	1,110	3	1 (Ref.)	
	Ever	8,479	9	0.4 (0.10-1.58)	
Age at menarche					0.841
≤11	Never	5,080	6	1 (Ref.)	
	Ever	10,228	11	0.96 (0.33-2.81)	
12-13	Never	13,437	17	1 (Ref.)	
	Ever	27,117	40	1.25 (0.69-2.28)	
≥14	Never	6,799	10	1 (Ref.)	
	Ever	12,674	17	1.07 (0.46-2.48)	
Age at menopause					0.125
≤44	Never	5,747	10	1 (Ref.)	
	Ever	15,615	14	0.58 (0.24-1.38)	

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TABLE 3. *(Continued)*

Subgroup	HT use	Cohorts	Cases	Model 2 HR (95% CI)	*P* for interaction
45-49	Never	6,425	7	1 (Ref.)	
	Ever	11,397	18	1.70 (0.67-4.29)	
≥50	Never	13,144	16	1 (Ref.)	
	Ever	23,007	36	1.30 (0.7-2.41)	
Ever been pregnant					0.761
Never	Never	2,075	4	1 (Ref.)	
	Ever	3,561	8	1.35 (0.38-4.79)	
Ever	Never	23,241	29	1 (Ref.)	
	Ever	46,458	60	1.14 (0.71-1.83)	

CI, confidence interval; HR, hazard ratio; HT, hormone therapy; NA, not available; Ref., reference.

Model 2 was adjusted for age (continuous), race, marital, education, body mass index, cigarette smoking history, personal history of cancer (except glioma), oral contraceptive use, hysterectomy, ovariectomy, ever been pregnant, age at menarche, and age at menopause.

usage less than 5 years, 0.49 (0.19-1.28) for 6-9 years of use, and 1.29 (0.72-2.28) for more than 10 years of use.

DISCUSSION

In this large cohort of 75,335 women, 101 cases of glioma were identified over a median follow-up period of approximately 11.82 years. Compared with nonusers, users of HT were not significantly associated with glioma risk. When accounting for HT status and duration of use, similar findings with no significant associations were identified.

Fourteen studies have evaluated the effect of HT on women's glioma risk.[4-10,12-18] In retrospective case-control studies, an inverse association with HT use and glioma was reported across all studies,[4-9,12] although some findings were not statistically significant.[6,7,9] Conversely, studies that collected HT exposure data prospectively found no significant association.[10,13-18] Our current study aligns with most previous prospective research, showing a non-significant increase in glioma risk among women who used HT. Two main factors may explain these inconsistencies across the studies. First, potential recall and selection bias in retrospective studies could have influenced the results. Second, these studies did not differentiate between the various components of HT. To our knowledge, five studies have specifically examined the impact of HT components on glioma risk.[10,14,16-18] In the Million Women Study and the UK General Practice Research Database, users of estrogen-only HT were found to be at a higher risk of glioma, while no such association was observed in users of estrogen-progestagen HT.[14,17] Additionally, a nationwide cohort of 789,901 Danish women, followed over 19 years, showed that progestin-only HT use was associated with an increased risk of potentially glioma risk.[18] However, two other studies found no notable heterogeneity between progestin users and estrogen users, with no significant association.[10,16] Previous evidence indicates that the expression of estrogen and progesterone receptors in gliomas varies, with progesterone receptor expression increasing in more malignant astrocytomas.[30] Furthermore, studies have shown that both exogenous estrogen and progesterone play dual roles in the key hallmarks of glioblastoma cells in vitro.[31,32] For instance, physiological levels of progesterone promote proliferation, invasion, and migration of glioma cells, while higher doses inhibit proliferation and induce cell death.[32] Thus, women exposed to different HT components may face varying risks of glioma, highlighting the need for further research focused on specific hormone types and dose.

In the PLCO study, participants who used HT more frequently had education beyond high school, a history of hysterectomy and/or oophorectomy, prior use of OC, and experienced menopause at a later age. Subgroup analysis showed a significant increased risk of glioma was identified in women with college graduate or more level, but not in those with an education level of some colleague or post high school or less. Further interaction analysis yielded no significant difference in education subgroup (P for interaction = 0.056). Similarly, initial analysis showed that there was a statistically significant interaction effect for ovariectomy and HT on the glioma risk (P for interaction = 0.028). However, after applying Bonferroni correction for multiple comparisons, the interaction effect was not significant for ovariectomy and HT ($P > 0.0056$). For other factors (OC, BMI, hysterectomy, marital status, age at menarche and menopause, and ever been pregnant), no significant results were identified for HT and glioma. Of note, these results may be chance findings due to the limited number of cases within each stratum. However, education reflects more complex socioeconomic factors and may also impact the decision to use HT. Thus, an association between HT, education, or ovariectomy could influence glioma incidence and thus should be included in future studies.

Two types of HT exposure that are of concern are "current use" and "past/former use," which have been investigated in six studies.[6,10,14-18] In the large San Francisco Bay Area Adult Glioma Study, Felini et al found a significant reduction in glioma risk, but only among current users, not former users.[8] However, other studies did not observe significant differences between these groups.[6,14-18] Notably, the studies used different exposure periods before the index date, ranging from 0 to 5 years,[10,14,17,18] which suggests that these findings should be interpreted with caution.

Another important issue is the cumulative duration of HT use and its potential association with glioma risk. Consistently, both prior research and our own, failed to demonstrate a time-independent relationship exists between duration of HT use and glioma.[6-8,10,12-18] Evaluating dose-response relationships

in observational studies is crucial for determining causality between long-term exposure and disease. Therefore, whether a dose-response association exists between HT use and glioma risk remains a subject of ongoing investigation.

Strengths of the present study include collecting HT data prospectively, longer time of follow-up, and comprehensive analysis, including a great number of covariates consideration, subgroup and interactions analysis, and sensitivity analyses. However, several limitations deserve attention. First, the statistical power of our findings may be constrained due to the small number of glioma cases identified in the study. Noteworthy, gliomas are relatively rare tumors, particularly among women, with an age-standardized incidence rate of only 4.61 per 100,000 person-years.[33] Second, we were unable to evaluate the effects of specific hormone types on glioma risk, as the female-specific questionnaire lacked detailed data on estrogen and progesterone levels. Finally, while we accounted for a considerable number of covariates, the potential for residual confounding remains a concern.

CONCLUSIONS

In conclusion, findings from the PLCO study indicate that HT use is not significantly associated with glioma risk. To confirm this relationship, future studies with larger sample sizes, prospective design, and extended follow-up periods are necessary, with particular focus on the specific components of HT and cumulative duration of use.

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REFERENCES

1. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: primary brain and other central nervous system tumors diagnosed in the United States in 2016-2020. *Neuro Oncol* 2023;25(12 Suppl 2):iv1-iv99. doi: 10.1093/neuonc/noad149
2. Ostrom QT, Coleman W, Huang W, et al. Sex-specific gene and pathway modeling of inherited glioma risk. *Neuro Oncol* 2019;21:71-82. doi: 10.1093/neuonc/noy135
3. Francis SS, Ostrom QT, Cote DJ, Smith TR, Claus E, Barnholtz-Sloan JS. The epidemiology of central nervous system tumors. *Hematol Oncol Clin North Am* 2022;36:23-42. doi: 10.1016/j.hoc.2021.08.012
4. Schlehofer B, Blettner M, Preston-Martin S, et al. Role of medical history in brain tumour development. Results from the international adult brain tumour study. *Int J Cancer* 1999;82:155-160. doi: 10.1002/(sici)1097-0215(19990719)82:2<155::aid-ijc1>3.0.co;2-p
5. Huang K, Whelan EA, Ruder AM, et al. Reproductive factors and risk of glioma in women. *Cancer Epidemiol Biomarkers Prev* 2004;13:1583-1588.
6. Hatch EE, Linet MS, Zhang J, et al. Reproductive and hormonal factors and risk of brain tumors in adult females. *Int J Cancer* 2005;114:797-805. doi: 10.1002/ijc.20776
7. Wigertz A, Lönn S, Mathiesen T, Ahlbom A, Hall P, Feychting M, Swedish Interphone Study Group. Risk of brain tumors associated with exposure to exogenous female sex hormones. *Am J Epidemiol* 2006;164:629-636. doi: 10.1093/aje/kwj254
8. Felini MJ, Olshan AF, Schroeder JC, et al. Reproductive factors and hormone use and risk of adult gliomas. *Cancer Causes Control* 2009;20:87-96. doi: 10.1007/s10552-008-9220-z
9. Wang SS, Hartge P, Yeager M, et al. Joint associations between genetic variants and reproductive factors in glioma risk among women. *Am J Epidemiol* 2011;174:901-908. doi: 10.1093/aje/kwr184
10. Andersen L, Friis S, Hallas J, Ravn P, Gaist D. Hormone replacement therapy and risk of glioma: a nationwide nested case-control study. *Cancer Epidemiol* 2013;37:876-880. doi: 10.1016/j.canep.2013.09.017
11. Anic GM, Madden MH, Nabors LB, et al. Reproductive factors and risk of primary brain tumors in women. *J Neurooncol* 2014;118:297-304. doi: 10.1007/s11060-014-1427-0
12. Krishnamachari B, Il'yasova D, Scheurer ME, Bondy ML, Wrensch M, Davis FG. A pooled multisite analysis of the effects of female reproductive hormones on glioma risk. *Cancer Causes Control* 2014;25:1007-1013. doi: 10.1007/s10552-014-0400-8
13. Silvera SA, Miller AB, Rohan TE. Hormonal and reproductive factors and risk of glioma: a prospective cohort study. *Int J Cancer* 2006;118:1321-1324. doi: 10.1002/ijc.21467
14. Benson VS, Pirie K, Green J, et al. Hormone replacement therapy and incidence of central nervous system tumours in the Million Women Study. *Int J Cancer* 2010;127:1692-1698. doi: 10.1002/ijc.25184
15. Michaud DS, Gallo V, Schlehofer B, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;19:2562-2569. doi: 10.1158/1055-9965.EPI-10-0447
16. Kabat GC, Park Y, Hollenbeck AR, Schatzkin A, Rohan TE. Reproductive factors and exogenous hormone use and risk of adult glioma in women in the NIH-AARP Diet and Health Study. *Int J Cancer* 2011;128:944-950. doi: 10.1002/ijc.25413
17. Benson VS, Kirichek O, Beral V, Green J. Menopausal hormone therapy and central nervous system tumor risk: large UK prospective study and meta-analysis. *Int J Cancer* 2015;136:2369-2377. doi: 10.1002/ijc.29274
18. Pourhadi N, Meaidi A, Friis S, Torp-Pedersen C, Mørch LS. Menopausal hormone therapy and central nervous system tumors: Danish nested case-control study. *PLoS Med* 2023;20:e1004321. doi: 10.1371/journal.pmed.1004321
19. Zhang GQ, Chen JL, Luo Y, et al. Menopausal hormone therapy and women's health: an umbrella review. *PLoS Med* 2021;18:e1003731. doi: 10.1371/journal.pmed.1003731
20. Zhang X, Du Y, Tan X, et al. The relationship between hormone replacement therapy and risk of kidney cancer in women: a meta-analysis. *Cancer Control* 2020;27:1073274820930194. doi: 10.1177/1073274820930194
21. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet* 2019;394:1159-1168. doi: 10.1016/S0140-6736(19)31709-X
22. Collaborative Group On Epidemiological Studies Of Ovarian Cancer, Beral V, Gaitskell K, Hermon C, Moser K, Reeves G, Peto R. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet* 2015;385:1835-1842. doi: 10.1016/S0140-6736(14)61687-1
23. Lan YL, Wang X, Lou JC, et al. Update on the effect of exogenous hormone use on glioma risk in women: a meta-analysis of case-control and cohort studies. *J Neurooncol* 2018;137:357-365. doi: 10.1007/s11060-017-2725-0
24. Alfuridy G, Alghamdi R, Alkhoshi A, et al. Does exogenous hormonal therapy affect the risk of glioma among females: a systematic review and meta-analysis. *Neurooncol Adv* 2023;6:vdad167. doi: 10.1093/noajnl/vdad167
25. Prorok PC, Andriole GL, Bresalier RS, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials* 2000;21(6 Suppl):273S-309S. doi: 10.1016/s0197-2456(00)00098-2
26. Shao C, Tang H, Wang X, He J, Wang P, Wu N. Oral contraceptive and glioma risk: a prospective cohort study and meta-analysis. *Front Public Health* 2022;10:878233. doi: 10.3389/fpubh.2022.878233
27. Shao C, Tang H, Wang X, He J, Wang P, Wu N. Body mass index and glioma risk: a prospective multicenter study. *Front Endocrinol (Lausanne)* 2022;13:933921. doi: 10.3389/fendo.2022.933921
28. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Int J Surg* 2014;12:1495-1499. doi: 10.1016/j.ijsu.2014.07.013
29. Srour B, Fezeu LK, Kesse-Guyot E, et al. Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ* 2019;365:l1451. doi: 10.1136/bmj.l1451
30. Tavares CB, Gomes-Braga FCSA, Costa-Silva DR, et al. Expression of estrogen and progesterone receptors in astrocytomas: a literature review. *Clinics (Sao Paulo)* 2016;71:481-486. doi: 10.6061/clinics/2016(08)12
31. Hirtz A, Rech F, Dubois-Pot-Schneider H, Dumond H. Astrocytoma: a hormone-sensitive tumor? *Int J Mol Sci* 2020;21:9114. doi: 10.3390/ijms21239114
32. Bello-Alvarez C, Camacho-Arroyo I. Impact of sex in the prevalence and progression of glioblastomas: the role of gonadal steroid hormones. *Biol Sex Differ* 2021;12:28. doi: 10.1186/s13293-021-00372-5
33. Lin D, Wang M, Chen Y, et al. Trends in intracranial glioma incidence and mortality in the United States, 1975-2018. *Front Oncol* 2021;11:748061. doi: 10.3389/fonc.2021.748061