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## SHORT REPORT

# Hormonal and reproductive factors and risk of glioma: A prospective cohort study

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The etiology of glioma, the most commonly diagnosed malignant brain tumor among adults in the United States, is poorly understood. Given the lower incidence rate of glioma in women than in men, it has been hypothesized that reproductive and hormonal factors may be involved in the etiology of glioma. We conducted a secondary analysis of data from the National Breast Screening Study, which included 89,835 Canadian women, aged 40–59 years at recruitment between 1980 and 1985. Linkages to national cancer and mortality databases yielded data on cancer incidence and deaths from all causes, respectively, with follow-up ending between 1998 and 2000. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals (CI) for the association between hormonal and reproductive factors and risk of glioma. During a mean of 16.4 years of follow-up, we observed 120 incident glioma cases. Compared with women with a relatively early age at menarche ( $\leq 12$  years), women who were 13–14 years of age at menarche had a 64% increased risk of glioma (95% CI = 1.01–2.65), and women who were older than 14 years of age at menarche had a 66% increased risk of glioma (95% CI = 0.86–3.20,  $P_{\text{trend}} = 0.06$ ). Age at first live birth, parity, menopausal status, use of oral contraceptive and use of hormone replacement therapy were not associated with altered glioma risk in our study population. Additional prospective studies are needed to confirm our findings.

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**Key words:** brain neoplasms; glioma; cohort; hormones; reproductive factors

Glioma is the most commonly diagnosed malignant brain tumor among adults in the United States,<sup>1,2</sup> with an estimated 5-year survival rate of 30%.<sup>2</sup> Currently, ionizing radiation is the only well-established risk factor for glioma.<sup>2,3</sup> Beyond this, few other risk factors for glioma have been established. However, incidence rates of glioma are lower in women than in men.<sup>2</sup> Furthermore, steroid hormone receptors, particularly androgen receptors, are expressed in gliomas,<sup>4,5</sup> and Khalid *et al.*<sup>6</sup> have demonstrated the expression of estrogen-receptor-related antigen in human glioma cells. As a result, it has been hypothesized that reproductive and hormonal factors may be involved in the etiology of glioma.

The epidemiologic literature regarding reproductive and hormonal factors and brain cancer risk is based primarily on case-control studies.<sup>7–12</sup> One cohort study, by Lambe *et al.*,<sup>13</sup> has also examined some of these associations. Parity has been examined as a risk factor for glioma in a number of studies, the findings for which have been mixed, with 5 observing no association<sup>7,9–12</sup> and 2 reporting inverse associations.<sup>8,13</sup> Of the 5 studies that have examined the role of age at first birth,<sup>8–10,13</sup> 3 observed no association<sup>9,10,13</sup> and 1, by Cantor *et al.*,<sup>8</sup> reported a statistically significant positive association, with risk of glioma. Additionally, no association has been found with menopausal status.<sup>7,9,11,12</sup> Few studies have described the association between other reproductive and hormonal factors and risk of glioma among women.<sup>7–13</sup> To our knowledge, the association between risk of glioma and age at menarche, menopausal status, use of oral contraceptives and hormone replacement therapy (HRT) use has not been examined in any prospective cohort studies. Given the current lack of data from prospective studies regarding these relationships, we examined the association between reproductive and hormonal factors and glioma risk in a cohort of Canadian women.

## Material and methods

### Study population

The design of our study has been described in detail elsewhere.<sup>14</sup> Briefly, 89,835 women, aged 40–59 years, were recruited into the Canadian National Breast Screening Study between 1980 and 1985 from the general Canadian population by various means, including personal invitation by letter, group mailings to employees of large institutions and to members of professional associations, advertisements in newspapers and public service announcements on radio and television.<sup>15</sup>

### Questionnaires

At recruitment into the cohort, participants completed self-administered questionnaires that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history and use of oral contraceptives and replacement estrogens. Specifically, participants were asked questions about their age at menarche, menopausal status, number of pregnancies lasting greater than 4 months (parity), age at first live birth, use of HRT and use of oral contraceptives. Women who reported having regular menstrual periods within the past 12 months were classified as premenopausal. Women whose menstrual periods ceased at least 12 months before enrollment into the study and those who had a bilateral oophorectomy were considered postmenopausal.<sup>16</sup>

### Ascertainment of incident glioma cases and deaths

Incident cases of glioma (ICD-M codes 9380/3–9473/3 and 9490/0–9506/0) and deaths from all causes were ascertained respectively by means of computerized record linkages to the Canadian Cancer Database and to the National Mortality Database, both of which are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality (to December 31, 2000) for women in Ontario, (December 31, 1998) for women in Quebec and (December 31, 1999) for women in other provinces. Table I provides information on the frequency of the different histologic subtypes of glioma in our study population.

### Statistical analysis

Of the 89,835 women recruited into the study, we excluded women with prevalent glioma at baseline ( $n = 5$ ), leaving 89,830 women available for analysis, amongst whom 120 incident cases of glioma were observed. Participants with prevalent cancers ( $n = 211$ ) at baseline were not excluded from the analyses. We ran the analyses with and without such subjects and the results were essentially the same. For these analyses, study participants were considered to be at risk from their date of enrollment until the date of diagnosis of glioma, the termination of follow-up (the date to

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TABLE I – DISTRIBUTION OF GLIOMA CASES BY MORPHOLOGY

| Morphology                              | n   |
|---|-----|
| Glioma, malignant                       | 2   |
| Mixed glioma                            | 2   |
| Astrocytoma NOS                         | 27  |
| Astrocytoma, anaplastic type            | 2   |
| Protoplasmic astrocytoma                | 1   |
| Gemistocytic astrocytoma                | 3   |
| Fibrillary astrocytoma                  | 2   |
| Glioblastoma NOS                        | 70  |
| Giant cell glioblastoma                 | 1   |
| Glioblastoma with sarcomatous component | 1   |
| Oligodendroglioma, NOS                  | 7   |
| Oligodendroglioma, anaplastic type      | 1   |
| Oligodendroblastoma                     | 1   |
| Total                                   | 120 |

TABLE II – BASELINE CHARACTERISTICS OF THE STUDY POPULATION

| Factor  | n = 89,830 |
|---|------------|
| Mean age at baseline (years)                      | 48.5 ± 5.6 |
| Mean age at menarche (years)                      | 12.8 ± 2.2 |
| Mean age at first live birth (years) <sup>1</sup> | 24.2 ± 4.8 |
| Parity (%)  |            |
| Nulliparous                                       | 14.4       |
| 1–2   | 35.5       |
| 3–4   | 38.4       |
| 5+  | 11.7       |
| Postmenopausal (%)                                | 43.2       |
| HRT use (% ever) <sup>2</sup>                     | 47.0       |
| Oral contraceptives use (% ever)                  | 58.5       |

<sup>1</sup>Among parous women only. <sup>2</sup>HRT, hormone replacement therapy; results among postmenopausal women only.

which cancer incidence data were available for women in the corresponding province) or death, whichever occurred earlier. Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the association between reproductive and hormonal factors and glioma risk. All multivariate models included terms for study center and randomization group (intervention or control). To test for trends in risk with increasing levels of the exposures of interest, we either assigned the categorical variables their ordinal number (parity) or the category median (age at menarche, age at first live birth, duration of oral contraceptive use and duration of HRT) and then fitted the assigned value of each risk factor as a continuous variable in the risk models. We then evaluated the statistical significance of the corresponding coefficient, using the Wald test.<sup>17</sup> Use of the lifetest procedure in SAS<sup>TM</sup> showed that the proportional hazards assumption fitted the models used. All analyses were performed using SAS version 9 (SAS Institute Cary, NC).

## Results

The average duration of follow-up for cohort members was 16.4 years (1,480,470 person-years). The mean (SD) age at baseline was 48.5 (5.6) (Table II) and the mean age at diagnosis for the cases was 60.0 (±7.1) years. Compared with noncases, glioma cases tended to be older, having an older mean age at menarche and were more likely to be postmenopausal at baseline (data not shown).

Table III shows that in age-adjusted models parity was not associated with altered risk of glioma. After multivariate adjustment, the HRs remained essentially unchanged. Likewise, menopausal status was not associated with glioma risk in both age- and multivariate-adjusted models. With respect to age at first birth, although being 30 years of age or older at first live birth was associated with a 32% increased risk of glioma, this finding was not statistically significant (95% CI = 0.69–2.50) (Table III). A statistically significant 64% increased risk of glioma was found for women who were 13–14 years of age at menarche compared with women who experienced menarche before 13 years of age after adjusting for age and other factors (95% CI = 1.01–2.65), and those with menarche after age 14 had a statistically nonsignificant 66% increase in risk (95% CI = 0.86–3.20); the associated test for trend in risk with increasing age at menarche was of borderline statistical significance ( $p_{\text{trend}} = 0.06$ ). Finally, exposure to exogenous estrogen from either oral contraceptive use or use of HRT was not associated with altered glioma risk (Table IV).

## Discussion

The etiology of glioma is largely unknown. Other than ionizing radiation, investigations have focused on the roles of lifestyle factors, such as diet, alcohol, and tobacco, and occupational exposures, but have not yielded consistent findings.<sup>2</sup> As indicated earlier, there is some evidence that hormonal factors might influence

glioma risk, which has prompted investigations in the relationship between hormonal and reproductive factors and glioma risk.

In the prospective study reported here, we found that risk of glioma increased with increasing age at menarche, a trend of borderline statistical significance. This supports findings by Hatch *et al.*<sup>9</sup> and Huang *et al.*,<sup>10</sup> both of whom observed positive associations between age at menarche and risk of glioma. Our results also are in keeping with evidence that age at menarche may be inversely associated with estrogen levels among both pre- and postmenopausal women<sup>18,19</sup> and that, in animal models, estrogens are neuroprotective, possibly *via* antioxidant effects or *via* activation of growth-signaling pathways.<sup>20,21</sup> In addition, estrogen has been shown to reduce glutamate toxicity in glial cells.<sup>22</sup> Exposure to estrogen due to early age at menarche may therefore act to protect against DNA damage to glial cells.

Of the 6 case-control studies<sup>7–12</sup> that have examined the relationship between parity and risk of glioma, 5 found no significant association<sup>7,9–12</sup> while one<sup>8</sup> observed a statistically significant inverse association. In addition, Lambe *et al.*,<sup>13</sup> who utilized linked registry data from the Swedish Cancer Registry and a nationwide Fertility Registry to conduct a nested case-control study (1,657 incident cases) of brain tumors within a cohort of 9,942 women, found a statistically significant reduced risk of glioma among ever-parous versus nulliparous women.

Our findings support the literature, which has largely found no association between age at first live birth<sup>10,13</sup> and risk of glioma. Hatch *et al.*<sup>9</sup> in contrast, observed a statistically significant positive trend with increasing age at first live birth. Our findings also support the literature, which has found no association between menopausal status<sup>7,9,11,12</sup> and risk of glioma. Further, our findings regarding use of oral contraceptives are consistent with those of Huang *et al.*,<sup>10</sup> who likewise reported no association. While we found no association between HRT and risk of glioma, Huang *et al.*<sup>10</sup> found a statistically significant inverse association (OR = 0.73, 95% CI = 0.49–1.10).

To our knowledge, ours is the first prospective cohort study to examine the association between a range of reproductive and hormonal factors, including parity, age at first live birth, age at menarche, menopausal status and exogenous hormone use, and risk of glioma. The main strength of this investigation is its prospective study design, which eliminates the possibility of recall bias. Also, the essentially complete follow-up of the cohort,<sup>23,24</sup> based on linkage to national cancer incidence and mortality databases, reduces the likelihood that our results reflect bias due to differential follow-up.

One limitation is the fact that information on menopausal status was collected only at baseline. Given that the minimum age at baseline was 40 and that participants were followed up for 16 years, on average, it is more likely that most of those who were premenopausal at enrollment would have become postmenopausal during the course of follow-up. Therefore, it is quite likely that our results for risk in association with premenopausal status at recruitment are largely accounted for by a mix of gliomas diag-

**TABLE III** – MULTIVARIATE-ADJUSTED HR AND 95% CI FOR THE ASSOCIATION BETWEEN REPRODUCTIVE AND MENSTRUAL FACTORS AND RISK OF INCIDENT BRAIN GLIOMAS

| Factor                         | Cases/person-years | Age-adjusted HR (95% CI) | Multivariate HR (95% CI) <sup>1,2</sup> |
|--------------------------------|--------------------|--------------------------|---|
| <b>Parity</b>                  |                    |                          |   |
| Nulliparous                    | 15/213,307         | 1.00 (Reference)         | N/A                                     |
| 1–2                            | 39/524,322         | 1.10 (0.60–2.00)         | 1.00 (Reference)                        |
| 3–4                            | 52/569,351         | 1.26 (0.70–2.24)         | 1.20 (0.75–1.92)                        |
| 5+                             | 14/172,164         | 0.99 (0.48–2.07)         | 0.90 (0.44–1.85)                        |
| <i>p</i> <sub>trend</sub>      |                    | 0.74                     | 0.97                                    |
| <b>Age at first live birth</b> |                    |                          |   |
| Nulliparous                    | 15/213,307         | 1.00 (Reference)         | N/A                                     |
| <23 years                      | 42/471,223         | 1.28 (0.70–2.32)         | 1.00 (Reference)                        |
| 23–25 years                    | 19/361,364         | 0.74 (0.37–1.45)         | 0.62 (0.35–1.13)                        |
| 26–29 years                    | 27/274,202         | 1.31 (0.70–2.48)         | 1.06 (0.61–1.83)                        |
| ≥30 years                      | 16/152,311         | 1.45 (0.72–2.94)         | 1.32 (0.69–2.50)                        |
| <i>p</i> <sub>trend</sub>      |                    | 0.45                     | 0.36                                    |
| <b>Age at menarche</b>         |                    |                          |   |
| ≤12 years                      | 37/601,668         | 1.00 (Reference)         | 1.00 (Reference)                        |
| 13–14 years                    | 64/690,372         | 1.60 (1.06–2.41)         | 1.64 (1.01–2.65)                        |
| >14 years                      | 18/188,430         | 1.59 (0.90–2.81)         | 1.66 (0.86–3.20)                        |
| <i>p</i> <sub>trend</sub>      |                    | 0.04                     | 0.06                                    |
| <b>Menopausal status</b>       |                    |                          |   |
| Pre                            | 46/727,102         | 1.00 (Reference)         | 1.00 (Reference)                        |
| Post                           | 59/542,142         | 1.17 (0.73–1.86)         | 1.31 (0.79–2.18)                        |

<sup>1</sup>Multivariate adjusted for age (continuous), study center, randomization group (intervention vs. control) and all other variables shown in the table among parous women only. <sup>2</sup>Likelihood ratio  $\chi^2 = 27.2$ ,  $df = 23$ ,  $p = 0.25$ .

**TABLE IV** – MULTIVARIATE-ADJUSTED HR AND 95% CI FOR THE ASSOCIATION BETWEEN EXOGENOUS HORMONE USE AND RISK OF INCIDENT BRAIN GLIOMAS

| Factor   | Cases/person-years | Age-adjusted HR (95% CI) | Multivariate HR (95% CI) <sup>1</sup> |
|--|--------------------|--------------------------|---------------------------------------|
| <b>Oral contraceptives<sup>2</sup></b>                         |                    |                          |                                       |
| Never  | 55/613,982         | 1.00 (Reference)         | 1.00 (Reference)                      |
| Ever   | 65/866,451         | 1.04 (0.72–1.50)         | 1.01 (0.68–1.52)                      |
| <b>Duration of oral contraceptive use<sup>2</sup></b>          |                    |                          |                                       |
| Never  | 55/613,982         | 1.00 (Reference)         | 1.00 (Reference)                      |
| 1–11 months  | 16/171,173         | 1.28 (0.73–2.24)         | 1.31 (0.72–40)                        |
| 12–35 months   | 10/195,102         | 0.73 (0.37–1.45)         | 0.85 (0.42–1.70)                      |
| 36–71 months   | 16/211,472         | 1.08 (0.62–1.91)         | 0.92 (0.48–1.76)                      |
| ≥72 months   | 23/288,755         | 1.04 (0.63–1.74)         | 1.01 (0.58–1.74)                      |
| <i>p</i> <sub>trend</sub>                                      |                    | 0.99                     | 0.82                                  |
| <b>Hormone replacement therapy<sup>1</sup></b>                 |                    |                          |                                       |
| Never  | 32/286,939         | 1.00 (Reference)         | 1.00 (Reference)                      |
| Ever   | 27/255,202         | 0.92 (0.54–1.55)         | 0.92 (0.55–1.56)                      |
| <b>Duration of hormone replacement therapy use<sup>1</sup></b> |                    |                          |                                       |
| Never  | 32/286,939         | 1.00 (Reference)         | 1.00 (Reference)                      |
| 1–35 months  | 13/117,274         | 1.00 (0.52–1.94)         | 1.00 (0.52–1.91)                      |
| ≥36 months   | 14/137,928         | 0.85 (0.44–1.63)         | 0.86 (0.45–1.65)                      |
| <i>p</i> <sub>trend</sub>                                      |                    | 0.65                     | 0.68                                  |

<sup>1</sup>Multivariate adjusted for age (continuous), study center, randomization group (intervention vs. control), parity, age at menarche (<12, 13–14, >14) and oral contraceptive use (ever/never) among postmenopausal women only. <sup>2</sup>Multivariate adjusted for age (continuous), study center, randomization group (intervention vs. control), parity, age at menarche (<12, 13–14, >14) and menopausal status.

nosed pre- and postmenopausally. Additionally, information on age at menopause was not collected, and we were, therefore, unable to examine the relationship between age at menopause and glioma risk. This may be of interest, given the possible association between age at menarche and glioma, which may indicate an effect of duration of exposure to endogenous hormones. Another limitation is that only limited behavioral and biologic data were collected beyond the recruitment date. As a result, we do not have information on postenrollment patterns of HRT use among premenopausal women, who became menopausal during follow-up, and only limited information on subsequent hormone use for women postmenopausal at enrollment.

In conclusion, the results of our study provide little support for associations between hormonal and reproductive factors and risk of glioma, with the possible exception of a positive association between age at menarche and risk. Additional prospective studies are needed to confirm our findings.

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