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SHORT REPORT

Cigarette smoking 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. N-nitroso compounds are known carcinogens, which are found in cigarette smoke and can induce gliomas in rats. On this basis, it has been hypothesized that cigarette smoking may be associated with an increased risk of glioma. We investigated the association between cigarette smoking and glioma risk in 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 hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between cigarette smoking and risk of glioma. During a mean of 16.4 years of follow-up, we observed 120 incident glioma cases. Among ever smokers, women who reported having quit smoking had a 51% increase in risk of glioma compared with never smokers (HR = 1.51, 95% CI = 0.97–2.34), while current smokers did not appear to have an increase in risk. When the association with former smokers was further examined by years since quitting, women who had quit smoking >10 years before baseline were at a decreased risk of glioma compared with women who had quit within the 10 years prior to baseline (HR = 0.55, 95% CI = 0.29–1.07), indicating that the association between former smokers and glioma may be driven by women, who recently quit smoking. Compared with nonsmokers, duration of cigarette smoking, number of cigarettes smoked per day and pack-years of smoking were associated with increased glioma risk, although the increases in risk were relatively modest. The present study provides some support for a positive association between cigarette smoking and risk of glioma.

Key words: brain neoplasms; glioma; cohort; smoking

Gliomas, which arise from neuroepithelial cells, are one of the 2 main histopathological types of brain tumor.[1] The etiology of glioma, the most commonly diagnosed malignant brain tumor among adults in the United States,[1,2] is not well understood. Indeed, there are few well-established risk factors for glioma beyond ionizing radiation,[1,3] male gender,[1] and possibly reproductive and menstrual factors.[4] In addition, it has been hypothesized that cigarette smoking may be involved in the etiology of glioma,[5] based on evidence that N-nitroso compounds, such as those found in cigarette smoke, have been shown to induce glioma in rats when administered intravenously.[6,7]

The epidemiologic literature regarding cigarette smoking and brain cancer risk is based primarily on case-control studies, all of which have found no association with ever smoking.[8–21] A recent cohort study by Efird *et al*.,[22] however, observed an increased risk of glioma in those who reported smoking greater than 2 packs of cigarettes per day. Given the limited data from prospective studies, we examined the association between smoking history 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.[23] 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.[24]

Questionnaires

At recruitment into the cohort, participants completed self-administered questionnaires that sought information on demographic characteristics and lifestyle factors. Information on smoking history was obtained from participants by asking them whether or not they had ever smoked; those who reported ever smoking were then asked to provide information on how many cigarettes they smoked per day, how many years they had smoked, and for former smokers, the year that they had ceased smoking.

Ascertainment of incident glioma cases and deaths from all causes

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 all-cause 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.

Statistical analysis

Of the 89,835 women recruited into the study, we excluded women with prevalent glioma at baseline ($n = 5$) and women for whom complete information on smoking history was not available ($n = 121$), leaving 89,709 women available for analysis, amongst whom 117 incident cases of glioma were observed. Participants with other prevalent cancers ($n = 211$) at baseline were not excluded from the analyses, because the results of analyses with and without such subjects were essentially the same.

For the analyses, study participants were considered to be at risk from their date of enrolment until the date of diagnosis of glioma (the outcome of interest), the termination of follow-up (the date to which cancer incidence data were available for women in the corresponding province) or death, whichever occurred earliest. 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 smoking history variables and glioma risk. Using the information on smoking history reported by the participants, we calculated age at the commencement of smoking for current smokers, by subtracting the number of years they reported smoking from their age at baseline, and for former smokers, by subtracting the number of years they reported smoking

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TABLE I – BASELINE CHARACTERISTICS OF THE STUDY POPULATION BY OUTCOME

	Cases of incident glioma (n = 117)	Noncases (n = 88,592)
Mean age (years)	50.4 (5.5)[1]	48.5 (5.6)
Mean education (years)	12.1 (2.9)	12.6 (3.1)
Mean body mass index (kg/m^2)	25.4 (4.3)	25.1 (4.7)
Parity (% parous)	87.5	85.6
Mean age at first live birth (years)	24.6 (5.0)	24.2 (4.7)
Mean age at menarche (years)	13.3 (3.0)	12.8 (2.2)
Menopausal status (% postmenopausal)	56.2	43.2
Smoking history (% ever)	49.7	48.9
Mean age started smoking[2]	23.1 (8.6)	22.7 (7.5)
Mean number of years smoked	21.5 (11.3)	19.0 (10.4)
Mean number of cigarettes smoked per day	18.2 (12.7)	16.7 (11.2)
Mean number of pack–years	22.4 (21.1)	18.3 (16.6)

[1]Values in parentheses indicate SDs.–[2]Results for smoking duration, intensity, pack–years and age started smoking are among ever smokers only.

from the age at which they stopped smoking. Cut points for smoking variables were determined *a priori* based on their distribution among smokers. All models included terms for study center and randomization group (intervention or control). In keeping with the literature,[10,20,22] multivariate analyses included additional adjustment for level of education (<high school, >high school) and body mass index (BMI). Multivariate models also included adjustment for reproductive factors (parity, age at first live birth, age at menarche and menopausal status), based on the evidence that these variables may be associated with glioma risk.[4,25,26] The cut points for all covariates were determined *a priori*. The cut points for BMI correspond to the National Institutes of Health guidelines, which classify BMI as normal weight (<25 kg/m^2), overweight (25–<30 kg/m^2) or obese (>30 kg/m^2). The cut points for all other covariates were based on the distribution of each of the variables at baseline. To test for trends in risk with increasing levels of the exposures of interest, we assigned the category median, 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.[27] Use of the lifetest procedure in SAS™ showed that the proportional hazards assumption was met in the fitted models. All analyses were performed using SAS version 9 (SAS Institute Cary, NC).

Results

The average duration of follow-up for cohort members was 16.5 years (1,462,004 person-years), and the mean (SD) age at diagnosis of the cases was 60.0 (7.1) years. Table I shows the distribution of demographic characteristics of the study population (collected at baseline), with case status at the end of follow-up. Cases tended to be slightly older at baseline than did noncases. Also, compared with noncases, cases were more likely to be parous, tended to have an older age at menarche, were more likely to be postmenopausal at baseline and reported slightly fewer years of cigarette smoking.

Table II shows that in adjusted models ever smoking was associated with a statistically nonsignificant 30% increase in risk of glioma. In addition, former smokers were at increased risk of glioma compared with never smokers (HR = 1.51, 95% CI = 0.97–2.34), while current smokers did not appear to be at increased risk (HR = 1.05, 95% CI = 0.62–1.78). Upon categorizing former smokers by years since having quit smoking, we found an inverse association between former smokers who quit >10 years prior to baseline compared with those who quit within the 10 years prior to baseline (HR = 0.39, 95% CI = 0.19–0.82) (data not shown). Compared with never smokers, there was some suggestion of an increase in risk with increasing number of years smoked (p_{trend} = 0.06). Risk also increased with number of cigarettes smoked per day (p_{trend} = 0.08) and pack-years of smoking (p_{trend} = 0.07). In addition, compared with never smokers, there was a 67% increase in risk among smokers who started smoking before the age of 20. When the tests for linear trend excluded the reference category (never smokers), the trends were similar for number of years smoked (p_{trend} = 0.06), number of cigarettes smoked per day (p_{trend} = 0.10), pack-years of smoking (p_{trend} = 0.14) and age started smoking (p_{trend} = 0.24) (data not shown).

TABLE II – MULTIVARIATE–ADJUSTED HAZARD RATIOS AND 95% CIs FOR THE ASSOCIATION BETWEEN CIGARETTE SMOKING AND RISK OF INCIDENT GLIOMA

Factor	Cases/person years	Multivariate[1]
Never smoked	59/751,385	1.00 (Reference)
Ever smoked	58/710,619	1.30 (0.88–1.93)[2]
Former smoker	38/392,746	1.51 (0.97–2.34)
Current smoker	20/317,874	1.05 (0.62–1.78)
Age started smoking (years)		
<20	19/236,482	1.67 (1.03–2.72)
20–21	18/228,978	0.85 (0.48–1.53)
>21	21/245,159	1.37 (0.71–2.65)
p_{trend}		0.63
Number of years smoked		
<10	17/228,081	0.55 (0.20–1.53)
11–20	16/233,722	1.19 (0.63–2.26)
>20	25/248,816	1.51 (0.97–2.34)
p_{trend}		0.06
Number of cigarettes/day		
<10	14/171,808	0.68 (0.31–1.50)
11–19	24/191,917	1.49 (0.86–2.61)
>19	20/346,894	1.44 (0.90–2.31)
p_{trend}		0.08
Pack–years		
<5	14/243,762	0.85 (0.46–1.58)
6–15	24/236,113	1.51 (0.83–2.75)
>15	20/230,744	1.50 (0.92–2.44)
p_{trend}		0.07

[1]Multivariate adjusted for age (time to event variable), education (<high school, >high school), body mass index (<25, 25–29, >30), parity (parous *vs*. nulliparous), age at first live birth (nulliparous, <20, 20–24, >24), age at menarche (<12, 13–14, >14), menopausal status, study center and allocation group.–[2]Values in parentheses indicate 95% CIs.

We also examined the associations after mutual adjustment for the smoking variables. For example, given that women who started smoking before age 20 had greater risk than those who started smoking at later ages, we examined the association between smoking duration and glioma risk after controlling for when women started smoking, since women who started smoking at younger ages were more likely to have smoked longer. Mutual adjustment did not significantly alter the association between smoking duration or age of smoking commencement and risk of glioma among smokers (data not shown). Mutual adjustment for both smoking duration (number of years smoked) and smoking intensity (cigarettes per day) among smokers attenuated the asso-

ciation between each of these variables and glioma risks somewhat (data not shown).

We were unable to fully examine the association between smoking history and glioma risk by histology (*e.g.*, glioblastoma, other astrocytoma and other glioma) given the small number of cases of other astrocytoma ($n = 34$) and other glioma ($n = 12$). For glioblastoma ($n = 71$), there were statistically significant positive associations with number of years smoked (HR for >20 years *vs.* never smokers = 2.66, 95% CI = 1.10–6.40, $p_{trend} = 0.02$), number of cigarettes smoked per day (HR for >19 cigarettes/day *vs.* never smokers = 2.86, 95% CI = 1.14–7.16, $p_{trend} = 0.07$) and pack-years of smoking (HR for >15 pack-years *vs.* never smokers = 2.52, 95% CI = 1.03–6.20, $p_{trend} = 0.04$) (data not shown).

Discussion

In the prospective study reported here, we found that ever having smoked cigarettes was associated with a modest increase in risk of glioma. In addition, women who reported being former smokers were at increased risk of glioma compared with never smokers, while current smokers did not appear to be at an increased risk. However, after categorizing former smokers by years since having quit smoking, we found an inverse association between former smokers who quit >10 years prior to baseline compared with those who quit within the 10 years prior to baseline, indicating that the association between former smokers and glioma may have been driven by women who recently quit smoking. Other aspects of cigarette smoking, including greater smoking intensity and duration, were also associated with modest increases in glioma risk.

The mechanism by which cigarette consumption might increase risk of glioma is unknown. Experimentally, intravenous administration of N-nitroso compounds has been shown to induce glioma formation in rats.[6] While there is evidence that these compounds can enter the brain during gestation (due to maternal cigarette smoking),[28] it is not known whether N-nitroso compounds from cigarette smoke cross the blood-brain barrier in adults. However, there is evidence that nicotine increases the permeability of the blood-brain barrier *in vivo*,[29] which may allow carcinogens, such as nitrosamines, to reach brain tissue.

Our findings differ from those of most studies to date, which have largely found no association between cigarette smoking and risk of glioma.[8–21] However, these were case-control studies, which are susceptible to selection and recall bias. In the only other prospective study to date, Efird *et al.*[22] analyzed data from a prospective cohort in California (130 incident cases) and, similar to our findings, they observed a 40% increase in risk for ever *versus* never smokers (95% CI = 1.0–2.1) and a 2-fold increase in risk of glioma among study participants who reported smoking greater than 2 packs per day compared with never smokers; the association between smoking and risk did not differ by type of cigarette (*e.g.,* filtered *versus* unfiltered, *etc.*), an aspect of smoking history that we were not able to examine.

The main strength of this investigation is its prospective study design, which eliminates the possibility of recall bias. As well, the essentially complete follow-up of the cohort,[30,31] based on linkage to national cancer incidence and mortality databases, reduces the likelihood that our results reflect bias due to differential follow-up. Although the number of incident cases of glioma in our study population was relatively small, it is similar to that in the study of Efird *et al.*,[22] the only previous prospective study to date. Our study is also limited, in which information on smoking was collected only at baseline, so that we were not able to take into account changes in cigarette use over time. Given that smoking rates are inversely associated with age,[32] it is quite likely that smoking habits would have changed over the course of follow-up, possibly leading to misclassification of exposure. However, such misclassification is quite likely to have been nondifferential, resulting in some attenuation of the associations.

In conclusion, the results of our study provide support for a positive association between cigarette smoking and risk of glioma. However, given that this is only the second prospective study to date, additional studies are needed.

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