Reproductive Factors and Risk of Meningioma and Glioma

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Abstract

Female sex hormones have previously been suggested as possible risk factors for brain tumors, but published studies have reported conflicting results. We conducted a population-based case-control study of glioma (n = 626) and meningioma (n = 906) cases and randomly selected controls stratified on age and geographic region (n = 1,774) in Denmark, Finland, Norway, Sweden, and the United Kingdom. Unconditional logistic regression was used to estimate odds ratios (OR) for glioma and meningioma in relation to reproductive factors. A decreased glioma risk was associated with ever-pregnancy compared with never-pregnancy [OR, 0.8; 95% confidence interval (95% CI), 0.6-1.0]. Meningioma risk among women ages <50 years was increased in relation to number of pregnancies leading to a live birth (OR, 1.8; 95% CI: 1.1-2.8 for giving birth to 3 children compared with nulliparous women; P_{trend} among parous women = 0.01). This relation was not found for older women. Breast-feeding among parous women increased the glioma risk (OR, 2.2; 95% CI, 1.3-3.9 for breast-feeding 36 months or more compared with breast-feeding 3 months or less). Menopausal status and age at menopause were not associated with meningioma or glioma risk. Our findings imply that reproductive hormones may influence the occurrence of meningioma and glioma. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2663–70)

Introduction

There is some evidence implying that sex hormones can be of importance for brain tumor etiology. The higher incidence of meningioma in women than men, with the highest ratio (2-3:1) during the reproductive years (1, 2), supports this hypothesis. An association between breast cancer and meningioma has been reported, with an elevated risk of meningioma among women with a previous diagnosis of breast cancer and an elevated risk of breast cancer among women with a previous diagnosis of meningioma (3, 4), suggesting common genetic or environmental risk factors. The incidence of glioma is, in contrast, ~1.5 times greater in men than women (2, 5). The higher incidence in men becomes evident around the age of female menarche, reaching a maximum around the age of menopause and diminishing thereafter (6). Progesterone, estrogen, and androgen receptors are expressed in meningiomas (7-9) and gliomas (10, 11) in various degrees. Use of exogenous female sex hormones has been reported in relation to meningioma and glioma risk with inconsistent results (12-15).

Because little is known of the etiology of brain tumors and current knowledge of how reproductive factors influence the risk is conflicting (12, 13, 16-27), we conducted an international population-based case-control study to investigate how reproductive history affects the risk of glioma and meningioma. Brain tumor growth and especially the growth of meningiomas has been reported to be related to pregnancy (28); therefore, we decided to investigate if the relations between pregnancy related factors and brain tumor risk differed between young (fertile ages) and older women.

Materials and Methods

Study Setting and Period. The study was conducted in Denmark nationwide, Finland excluding Northern Lapland and Åland, the southern and middle regions of Norway, the geographic areas in Sweden covered by the regional cancer registries in Stockholm, Göteborg, Umeå, and Lund, and the Thames regions of Southeast England. The study period was from September 2000 to February 2004, although the exact dates within this period varied by country. The study also contributed data on a subset of participants to the previously

Received 5/5/08; revised 7/7/08; accepted 7/15/08.

Grant support: Swedish Research Council and the Swedish Cancer Society. All partners were also supported by the European Union Fifth Framework Program "Quality of Life and Management of Living Resources" (contract number QLK4-CT-1999-01563), and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association. The provision of funds to the INTERPHONE study investigators via the UICC was governed by agreements that guaranteed INTERPHONE's complete scientific independence. These agreements are publicly available at http://www.iarc.fr/ENG/Units/RCAd.html.

Additional support was given to the Danish partner by the Danish Cancer Society. The Finnish partner received further financing from the Emil Aaltonen Foundation, and the Academy of Finland (grant #80921). The UK partner was also sponsored by the Mobile Telecommunications and Health Research Program. The views expressed in the publication are those of the authors and not necessarily those of the funders.

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doi:10.1158/1055-9965.EPI-08-0406

described INTERPHONE study (29). In Denmark, Finland, Norway, Sweden, and Southeast England, several additional questions were added to the INTERPHONE core protocol. A number of different issues were covered by detailed questions, including questions related to reproductive history. Results on exogenous female sex hormones and brain tumor risk have previously been reported for the Swedish data (14).

Case Ascertainment. Eligible cases were all women diagnosed during the study period with intracranial glioma [International Classification of Diseases tenth revision (ICD-10), code C71; International Classification of Diseases for Oncology second edition (ICD-O-2), 9380-9384, 9390-9394, 9400-9401, 9410-9411, 9420-9424, 9430, 9440-9443, 9450-9451, 9460, 9480-9481, and 9505 or intracranial meningioma (ICD-10, code C70, D32; ICD-O-2, codes 9530-9539).

The age range for inclusion differed slightly between the countries: ages 20 to 69 y in the Nordic countries and ages 18 to 59 y in the United Kingdom. Cases were identified continuously during the study period through collaboration with the treating clinics. The completeness of case ascertainment was verified through search in appropriate population-based cancer registries, and extra cases found during the study period were included in the study, except in Finland where the cancer registry was only checked afterwards for completeness without enrolling any additional patients. A reference date of diagnosis was defined as the first examination leading to diagnosis (usually the first radiological examination). Approval was sought on an individual basis from the attending physician to approach each case.

Control Selection. Controls from the Nordic countries were randomly selected from a population register of the total population of the study area, stratified on age (in 5-y groups), and geographic region. In the United Kingdom, controls were randomly selected, within stratum-matching, from the general practitioners' patient lists. These lists are a representative source of population-based controls as it has been estimated that 98% of the UK population is registered with a general practitioner (30).

Time of exposure was measured related to a reference date (for the cases the date of diagnosis). The reference dates for controls were constructed from the interview date of the control, with adjustment for the mean interval between the diagnostic and interview date of cases and the difference between the mean interview dates of cases and controls, to correct for the fact that controls were interviewed later than cases on average, thereby making reference dates comparable. The adjustments were done separately for each country and separately for glioma and meningioma cases. Glioma cases were on average interviewed 66 d earlier than the controls and meningioma cases on average interviewed 28 d earlier than the controls. The reference dates for glioma cases differed on average 4 d compared with the reference dates for controls and the reference date for meningioma cases differed 8 d compared with controls. The remaining minor differences are due to the construction of reference dates for controls originally also included men.

Data Collection. All cases and controls were invited to participate in the study as soon as possible after identification. All interviews and contacts were made by trained interviewers employed for this purpose. Data were collected through personal interviews using a computer program with questions read by the interviewer from a laptop computer screen. In Finland, however, answers were recorded on a paper copy of the questionnaire and later entered into the computer program. Almost half the interviews in Norway, but only a small minority elsewhere, were conducted over the telephone. If a case had died, the closest relative was contacted as a proxy respondent where possible, except in the United Kingdom where ethical agreement was only obtained for proxy interviews for patients who were too ill or deceased if a relative replied to the invitation letter on the patient's behalf. Each study was approved by the appropriate local ethics committee.

Exposure information was gathered through questions about menarche, menopause, pregnancies, and breastfeeding.

Statistical Analysis. Multivariate logistic regression models were used to compute odds ratios (OR) and 95% confidence intervals (CI). Data from each country were first analyzed separately (data not shown), followed by analyses of the pooled data adjusted for country. In case of heterogeneity in the country-specific results (defining heterogeneity conservatively as $P < 0.10$), we used a two-stage random effect method for the pooled analysis (31). Adjustments for the stratification variables (age, country, and region within country) and education were made in all analyses. Analyses were also made to investigate possible confounding from smoking, marital status, ever use of hormonal contraceptives and hormone replacement therapy, twin pregnancies, and previous radiotherapy. These variables did not affect the results and therefore were not included in the final models.

Tests for trend were done on the original values rather than on categorized values.

All analyses were done using SAS statistical software version 9.1 (32).

A woman was defined as postmenopausal if she had had a bilateral oophorectomy or if her menstruation had stopped at least 1 y before the reference date. Women who had had a hysterectomy without a bilateral oophorectomy when still premenopausal could not be directly assessed as premenopausal or postmenopausal.

Results

During the study period, 1,033 glioma cases, 1,213 meningioma cases, and 3,394 controls were identified. Participation rates were 61% (n = 626) for glioma cases (range, 36-81% between countries), 75% (n = 907) for meningioma cases (range, 58-88%), and 52% (n = 1,774) for controls (range, 43-69%). Proxy respondents were interviewed for 12% (n = 74) of participating glioma cases, 1.4% (n = 13) of participating meningioma cases, and <0.1% (n = 1) of participating controls. One patient diagnosed with meningioma had Turner's syndrome (having only one X chromosome) and was not included in the analyses (33). The characteristics of cases and controls are summarized in Table 1. Glioma cases had a higher representation in younger age groups than the meningioma cases. The controls were recruited stratified

Table 1. Characteristics of glioma and meningioma cases and controls; Nordic-UK Brain Tumor Study 2000 to 2004

Characteristic	Glioma cases (n = 626)	Meningioma cases (n = 906)	Controls (n = 1,774)
	No (%)	No (%)	No (%)
Country			
Denmark	107 (17)	124 (14)	423 (24)
Finland	127 (20)	264 (29)	505 (28)
Norway	117 (19)	155 (17)	182 (10)
Sweden	145 (23)	193 (21)	328 (18)
United Kingdom	130 (21)	170 (19)	336 (19)
Age at reference date (y)*			
18-29	72 (12)	16 (2)	135/133 (8/7)
30-39	119 (19)	99 (11)	241/244 (14/14)
40-49	140 (22)	221 (24)	428/425 (24/24)
50-59	176 (28)	368 (41)	583/585 (33/33)
60-	119 (19)	202 (22)	387/387 (22/22)
Education†			
Compulsory school	191 (31)	315 (35)	534 (30)
Vocational/secondary	162 (26)	218 (24)	448 (25)
Upper secondary	126 (20)	175 (19)	419 (24)
University	144 (23)	194 (21)	368 (21)
Unknown	3 (0.5)	4 (0.4)	5 (0.3)
Marital status			
Single	89 (14)	78 (9)	199 (11)
Married	450 (72)	645 (71)	1,276 (72)
Divorced	64 (10)	119 (13)	206 (12)
Widowed	19 (3)	60 (7)	91 (5)
Unknown	4 (0.6)	4 (0.4)	2 (0.1)

*Numbers and percentages vary for controls because of the use of different reference dates in analyses of glioma or meningioma.
† Highest education completed.

on the ages of all cases, and therefore, the age distribution among controls primarily reflects the distribution among cases overall.

Glioma. There was no association between age at menarche and glioma risk overall (Table 2), and no association for early, normal, or late menarche when age groups were examined separately, but a significant trend (P_{trend} = 0.03) for increasing age at menarche related to increasing risk of glioma at ages <50 years, although there was no significant heterogeneity between age groups (P = 0.08; Table 3). Menopausal status and age at menopause did not influence glioma risk (Table 2). When women with unknown menopausal status were included in the analysis of menopausal status as postmenopausal if ages ≥60 years and premenopausal if ≤40 years, results did not change (data not shown). Women who had ever been pregnant had a borderline significantly lower risk of glioma (OR, 0.8; 95% CI, 0.6-1.0) than women who had never been pregnant, and there was a significant trend for decreasing risk associated with number of pregnancies (P_{trend} = 0.02 among ever pregnant women; Table 2).The indication of a protective effect of ever-pregnancy was evident only for women ages <50 years, although no trend with number of pregnancies was seen in this age group. For women ages ≥50 years, a significant trend related to number of pregnancies was seen. This trend was, however, driven by being pregnant five or more times, which very few glioma cases had been (Table 3). Ever having had a live birth and number of pregnancies resulting in a live birth were not associated with glioma risk (Tables 2-3), but after adjustment for breast-feeding duration, a significant protective trend in risk with increasing number of pregnancies was found (data not shown). Women giving birth at age ≥35 years for the first time had an increased glioma risk compared with women giving birth before the age of 20 years (OR, 1.8; 95% CI, 1.0-3.4), although there was no statistically significant trend of risk with age at first birth (P = 0.5). Among parous women, increasing duration of breast-feeding increased the risk of glioma; women who had breast-fed for ≥36 months in total had an OR of 2.2 (95% CI, 1.3-3.9) compared with women who had breast-fed ≤3 months (P_{trend} = 0.003; Table 2). The raised risk associated with duration of breast-feeding was most distinct for older women, but the same pattern was also suggested (nonsignificantly) for women ages <50 years, and there was no heterogeneity in the results between the two age groups (P = 0.3; Table 3).

Reanalyzing the data only including histologically confirmed cases (96% of participating cases) did not change the results. Results from separate analyses of glioblastoma risk did not differ appreciably from results for glioma overall except for a slightly higher OR associated with giving birth for the first time at age ≥35 years (OR, 2.6; 95% CI, 1.1-6.6). Glioblastoma cases were on average 9 years older at diagnosis than nonglioblastoma glioma cases.

Excluding proxy answers from the analyses did not change the results except for the breast-feeding analysis where the OR changed from 2.2 (95% CI, 1.3-3.9) to 1.7 (95% CI, 0.9-3.1) for breast-feeding ≥36 months (P = 0.04).

Meningioma. Age at menarche, menopausal status, and age at menopause were not associated with meningioma risk (Table 2). When women with unknown menopausal status where included in the analysis of menopausal status as postmenopausal if age ≥60 years

and premenopausal if age ≤40 years, the results did not change (data not shown). Ever being pregnant, number of pregnancies, or number of pregnancies leading to a live birth were not related to meningioma risk for women overall (Table 2). Stratifying the women according to age revealed an increasing meningioma risk associated with number of live births: P_{trend} among those ever having a live birth was 0.01, for women ages <50 years. This was

Table 2. Risks of glioma and meningioma in relation to reproductive factors; Nordic-UK Brain Tumor Study 2000 to 2004

Reproductive factor	Glioma cases	Controls	OR (95% CI)*	Meningioma cases	Controls	OR (95% CI)*
Age at menarche (y)						
<12	80	225	1.0	117	225	1.0
12-13	264	853	0.9 (0.6-1.2)	409	853	0.9 (0.7-1.2)
≥14	207	674	0.9 (0.7-1.3)	347	674	0.9 (0.7-1.2)
Missing	75	22	P_{trend} = 0.4	33	22	P_{trend} = 0.6
Menopausal status						
Premenopausal	309	835	1.0	333	833	1.0
Postmenopausal	205	737	1.1 (0.7-1.9) †	426	739	1.0 (0.8-1.3)
Unknown due to hysterectomy	38	131		92	131	
Unknown due to other reasons	74	71		55	71	
Age at menopause (y) ‡						
<47	53	179	1.0	113	179	1.0
47-52	106	384	1.0 (0.6-1.4)	226	385	0.9 (0.7-1.2)
≥53	42	169	0.9 (0.6-1.5)	81	170	0.8 (0.5-1.2)
Missing	4	5	P_{trend} = 0.3	6	5	P_{trend} = 0.3
Ever pregnant						
No	117	247	1.0	103	247	1.0
Yes	503	1,519	0.8 (0.6-1.0)	796	1,519	1.1 (0.8-1.4)
Missing	6	8		7	8	
No of pregnancies						
0	117	247	1.0	103	247	1.0
1	80	218	0.8 (0.6-1.2)	82	218	0.8 (0.6-1.1)
2	187	494	0.9 (0.7-1.2)	267	494	1.1 (0.9-1.5)
3	122	413	0.7 (0.5-1.0)	239	413	1.2 (0.9-1.6)
4	70	228	0.7 (0.5-1.1) †	114	228	1.0 (0.7-1.5)
≥5	32	159	0.5 (0.2-1.1) †	89	159	1.1 (0.8-1.6)
Missing	18	15	P_{trend} = 0.005 P_{trend} among ever pregnant = 0.02	12	15	P_{trend} = 0.09 P_{trend} among ever pregnant = 0.08
Ever had live birth						
No	143	319	1.0	127	319	1.0
Yes	480	1,449	0.9 (0.7-1.1)	775	1,449	1.2 (0.9-1.5)
Missing	3	6		4	6	
No of pregnancies leading to a live birth						
0	143	319	1.0	127	319	1.0
1	92	299	0.8 (0.5-1.0)	129	299	0.9 (0.6-1.4) †
2	252	701	0.9 (0.7-1.2)	380	701	1.2 (0.9-1.6)
3	101	325	0.9 (0.5-1.4) †	198	325	1.3 (1.0-1.8)
≥4	35	124	0.8 (0.5-1.2)	68	124	1.1 (0.8-1.6)
Missing	3	6	P_{trend} = 0.4 P_{trend} among ever live birth = 0.8	4	6	P_{trend} = 0.05 P_{trend} among ever live birth = 0.09
Age at first live birth (y)						
<20	39	146	1.0	85	146	1.0
20-24	173	556	1.3 (0.9-2.0)	319	556	1.1 (0.8-1.5)
25-29	148	485	1.3 (0.8-2.0)	232	485	0.9 (0.5-1.5) †
30-34	60	193	1.3 (0.8-2.1)	74	193	0.7 (0.5-1.1)
≥35	23	53	1.8 (1.0-3.4)	41	53	1.4 (0.8-2.3)
Missing	37	16	P_{trend} = 0.5	24	16	P_{trend} = 0.2
Breast feeding (mo) §						
≤3	94	369	1.0	193	369	1.0
4-11	139	493	1.1 (0.8-1.5)	246	493	0.9 (0.7-1.2)
12-23	114	368	1.3 (0.9-1.8)	202	368	1.0 (0.7-1.3)
24-35	40	112	1.7 (1.0-2.7)	62	112	1.0 (0.6-1.4)
≥36	32	73	2.2 (1.3-3.9)	33	73	0.8 (0.5-1.3)
Missing	61	34	P_{trend} = 0.003	39	34	P_{trend} = 0.6

*Adjusted for age, country, region within country, and education.
† Results obtained from two-stage random effect model, due to heterogeneity, $P < 0.1$.
‡ The age at menopause was calculated as the age when the periods stopped or of bilateral oophorectomy, which ever came first.
§ Only parous women. Adjusted for age, country, region within country, education, and number of live births.

Table 3. Risks of glioma and meningioma by age in relation to reproductive factors; Nordic-UK Brain Tumor Study 2000 to 2004

Reproductive factor	Glioma						Meningioma					
	<50 y			≥50 y			<50 y			≥50 y		
	No cases	No controls*	OR (95% CI) [†]	No. cases	No. controls*	OR (95% CI) [†]	No. cases	No. controls*	OR (95% CI) [†]	No. cases	No. controls*	OR (95% CI) [†]
Age at menarche (y)												
<12	45	115	1.0	35	110	1.0	58	115	1.0	59	110	1.0
12-13	157	436	1.0 (0.7-1.5)	107	417	0.7 (0.4-1.1)	172	434	0.8 (0.5-1.1) [‡]	237	419	1.0 (0.7-1.5)
≥14	107	249	1.3 (0.8-2.0)	100	425	0.6 (0.4-1.0)	100	249	0.7 (0.4-1.4) [‡]	247	425	1.1 (0.8-1.7)
Missing	22	4	P_{trend} = 0.03	53	18	P_{trend} = 0.2	6	4	P_{trend} = 0.7	27	18	P_{trend} = 1.0
Ever pregnant												
No	100	166	1.0	17	81	1.0	49	165	1.0	54	82	1.0
Yes	227	636	0.7 (0.5-1.0)	276	883	1.4 (0.8-2.4)	285	635	1.0 (0.7-1.5)	511	884	0.9 (0.6-1.3)
Missing	4	2		2	6		2	2		5	6	
No of pregnancies												
0	100	166	1.0	17	81	1.0	49	165	1.0	54	82	1.0
1	41	101	0.7 (0.4-1.1)	39	117	1.5 (0.8-2.9)	34	101	0.9 (0.5-1.5)	48	117	0.6 (0.4-1.1)
2	77	218	0.7 (0.5-1.1)	110	276	1.8 (1.0-3.2)	90	217	1.0 (0.6-1.5)	177	277	1.0 (0.7-1.5)
3	50	163	0.6 (0.4-0.9)	72	250	1.3 (0.7-2.4)	87	163	1.2 (0.8-1.9)	152	250	0.9 (0.6-1.4)
4	33	83	0.8 (0.5-1.4)	37	145	1.1 (0.6-2.2)	39	83	1.1 (0.6-1.9)	75	145	0.8 (0.5-1.3)
≥5	20	70	0.6 (0.3-1.1)	12	89	0.5 (0.2-1.2)	34	70	1.0 (0.6-1.8)	55	89	0.9 (0.6-1.6)
Missing	10	3	P_{trend} = 0.4 P_{trend} among ever pregnant = 0.6	8	12	P_{trend} = 0.01 P_{trend} among ever pregnant = 0.0004	3	3	P_{trend} = 0.2 P_{trend} among ever pregnant = 0.1	9	12	P_{trend} = 0.8 P_{trend} among ever pregnant = 0.5
Ever had live birth												
No	118	215	1.0	25	104	1.0	60	214	1.0	67	105	1.0
Yes	211	589	0.8 (0.6-1.1)	269	860	1.2 (0.8-2.0)	275	588	1.3 (0.9-1.8)	500	861	0.9 (0.7-1.3)
Missing	2	0		1	6		1	0		3	6	
No of pregnancies leading to a live birth												
0	118	215	1.0	25	104	1.0	60	214	1.0	67	105	1.0
1	43	136	0.6 (0.4-1.0)	49	163	1.2 (0.7-2.1)	50	136	1.1 (0.7-1.7)	79	163	0.7 (0.5-1.1)
2	113	308	0.9 (0.6-1.2)	139	393	1.4 (0.8-2.3)	129	307	1.1 (0.8-1.7)	251	394	1.0 (0.7-1.4)
3	42	110	0.9 (0.6-1.5)	59	215	1.1 (0.6-1.8)	71	110	1.8 (1.1-2.8)	128	215	0.9 (0.6-1.4)
≥4	13	35	0.9 (0.4-1.9)	22	89	0.9 (0.5-1.8)	25	35	1.7 (0.9-3.2)	42	89	0.8 (0.5-1.3)
Missing	2	0	P_{trend} = 1.0 P_{trend} among ever live birth = 0.2	1	6	P_{trend} = 0.5 P_{trend} among ever live birth = 0.2	1	0	P_{trend} = 0.008 P_{trend} among ever live birth = 0.01	3	6	P_{trend} = 0.8 P_{trend} among ever live birth = 0.9
Age at first live birth (y)												
<20	16	45	1.0	23	101	1.0	26	45	1.0	59	101	1.0
20-24	64	187	1.2 (0.6-2.3)	109	369	1.5 (0.9-2.5)	102	187	1.1 (0.6-2.0)	217	369	1.1 (0.7-1.6) [‡]
25-29	65	229	1.0 (0.5-2.0)	83	256	1.5 (0.9-2.7) [‡]	85	228	0.8 (0.5-1.5)	147	257	0.9 (0.5-1.9)
30-34	39	100	1.4 (0.7-2.9)	21	93	1.1 (0.3-4.2)	37	100	0.8 (0.4-1.5)	37	93	0.7 (0.4-1.1)
≥35	14	23	2.4 (0.9-6.1)	9	30	1.5 (0.6-3.7)	19	23	1.7 (0.7-3.8)	22	30	1.2 (0.6-2.3)
Missing	13	5	P_{trend} = 0.4	24	11	P_{trend} = 0.9	6	5	P_{trend} = 0.4	18	11	P_{trend} = 0.4
Breast feeding (mo)[§]												
≤3	35	118	1.0	59	251	1.0	56	118	1.0	137	251	1.0
4-11	64	188	1.2 (0.7-2.1)	75	305	1.1 (0.7-1.7)	64	188	0.8 (0.5-1.3)	182	305	1.0 (0.7-1.3)
12-23	56	176	1.3 (0.7-2.3)	58	192	1.4 (0.9-2.3)	91	175	1.2 (0.7-1.9)	111	193	0.9 (0.7-1.4)
24-35	21	57	1.5 (0.7-3.2)	19	55	1.9 (1.0-3.7)	33	57	1.2 (0.6-2.3)	29	55	0.8 (0.5-1.5)
≥36	17	40	1.9 (0.8-4.2)	15	33	2.7 (1.2-6.0)	20	40	0.9 (0.4-1.8)	13	33	0.7 (0.3-1.4)
Missing	18	10	P_{trend} = 0.3	43	24	P_{trend} = 0.002	11	10	P_{trend} = 0.6	28	24	P_{trend} = 0.1

*Numbers vary for controls because of the use of different reference dates in analyses of glioma or meningioma.

[†] Adjusted for age, country, region within country, and education.

[‡] Results obtained from two-stage random effect model, due to heterogeneity, $P < 0.1$.

[§] Only parous women. Adjusted for age, country, region within country, education, and number of live births.

not seen for older women, *P* value for heterogeneity between age groups was 0.01 (Table 3). Breast-feeding and age at first live birth were not associated with meningioma risk (Tables 2-3).

Reanalyzing the data including only the histologically confirmed cases (90% of participating cases) did not change the results. Excluding proxy answers from the analyses did not alter the results.

Discussion

In this large population-based case-control study, we found an inverse association between glioma risk and number of pregnancies and an elevated glioma risk associated with breast-feeding. There was no association between age at menarche and glioma risk overall, but a significant trend for increasing age at menarche related to increasing glioma risk for ages <50 years when age groups were examined separately. For meningioma, an increasing risk was associated with number of pregnancies leading to live births among women ages <50 years, but this was not found among older women or for the total number of pregnancies overall. Menopausal status and age at menopause were not related to either meningioma or glioma risk.

Previously reported studies have not shown a coherent picture concerning reproductive factors and brain tumor risk. Some studies have found an increasing glioma risk with increasing age at menarche (12, 13, 25), sometimes confined to postmenopausal women (25), which is contrary to our results. Menopausal status has been reported not associated with glioma risk (12, 13, 21), although one study found an increased glioma risk for postmenopausal women (23).

A decreased glioma risk associated with ever being parous and decreasing risks by number of pregnancies have been reported previously (12, 16, 19, 22). We found a protective effect only among younger women, but in this age group, there was no trend associated with number of pregnancies implying that the first pregnancy may be the most important and that subsequent pregnancies do not confer additional protection. A first pregnancy has a long-term effect on hormone levels. Parous women have lower levels of androgens, prolactin, and free estradiol and higher levels of sex hormone–binding globulin than nulliparous women (34-36). The trend observed for women ages ≥50 years was significant but was driven by women with ≥5 pregnancies, a finding that differed widely from the rest of the results, and should be interpreted with caution. The trend tests including never-pregnant women should also be treated cautiously because the data are nonlinear and a linear trend test may be inappropriate. No association was found between ever having a live birth or the number of live births and glioma risk, which seems inconsistent with the results for the number of pregnancies. However, as we found an increased risk of glioma associated with duration of breast-feeding, this might have confounded the results observed for number of live births. Duration of breast-feeding should be more closely related to number of live births than to number of pregnancies; indeed, when adjusted for breast-feeding, we found a reduced glioma risk also for number of live births. Five studies have reported no association between parity and glioma risk (13, 17, 18, 21, 25); these studies did not adjust for breast-feeding.

The raised risk associated with duration of breast-feeding was most pronounced for older women, but the same pattern was also suggested (nonsignificantly) for women ages <50 years. The result was to some extent influenced by proxy answers, but after exclusion of these, the ORs were still increased and the significant trend still evident. Our results support findings from a previous study (25), although no effects has also been reported (12). The biological mechanism explaining how breast-feeding could increase glioma risk is unclear and it can be difficult to separate the effect of breast-feeding from other aspects of pregnancy. The hormones prolactin and oxytocin are increased during breast-feeding. They have been shown to have opposite effects on human glioma cells, with prolactin inducing cellular growth and mitogenesis (37) and oxytocin being able to inhibit cell proliferation (38). Breast-feeding can delay the reestablishment of normal ovulation by 6 to 9 months (39), and thereby reduce the cumulative time of estrogen exposure.

Meningioma risk increased with number of live births, but this was only found for women ages <50 years and only from 3 or more births. One potential explanation could be an effect of hormones on tumor growth rather than tumor initiation. Meningiomas are most often slow-growing, and it is possible that the raised levels of estrogens and progesterone during a pregnancy stimulate the growth of an already existing but asymptomatic tumor. No effect of parity was found among older women, which is consistent with the assumption that parity has a promotive effect. Progesterone and estrogen levels are dramatically raised during a pregnancy, especially during the latter part (40). We only found an association for the number of pregnancies leading to a live birth, but not for the number of pregnancies overall. The results for number of pregnancies could have been diluted by pregnancies interrupted at an early stage before the extreme increase of hormone levels. Previously published studies have not reported results separately for younger and older women and no significant results have been observed for parity (12, 22, 24, 26), although Jhawar et al. (24) reported some support for an increased risk for parous compared with nulliparous women.

Menopausal status was not associated with meningioma risk in our study as also reported by others (12, 23, 27), although both reduced risks (18, 24) and increased risks (20, 26) have also been reported. Most studies have not found any association with age at menarche (12, 20, 26, 27).

Analyses were made to investigate possible confounding from marital status, smoking, ever or never use of hormonal contraceptives and hormone replacement therapy, twin pregnancies, and prior radiotherapy treatment, but risk estimates were not changed by these adjustments. There might still be confounding from unknown risk factors, including genetic factors.

Misclassification of exposure history may occur, especially when self-reported information is used. This is probably a minor problem for exposures such as number of pregnancies leading to a live birth. Maternal recall of breast-feeding duration has been shown to be valid when it is recalled after a short period (≤3 years; ref. 41) but less valid for longer periods (42). The validity

of age of menarche reported by middle-aged women has been questioned in a study; however, validity was improved when age at menarche was categorized into three groups (43). A nondifferential misclassification of exposure will lead to a dilution of the risk estimates. Cases may, on the other hand, recall exposures differently than controls as a result of them having a tumor and thereby cause a biased result.

Nonparticipation is a potential source of selection bias. When cases and controls were initially informed about the study, the interest of the investigators in reproductive factors was not mentioned and the risk of bias therefore reduced. Age at menarche (44), age at first birth (45, 46), and breast-feeding patterns (47, 48) have been shown to be associated with socioeconomic status, and participation among controls is also related to socioeconomic status (49). The adjustment for education as an indicator of socioeconomic status should have reduced the effect of this potential bias. The results for meningioma and glioma risk differed in our study, which argues against a major problem of control selection bias as selection bias among controls would be expected to affect both tumor types similarly. Participation proportion differed between study centers, but there were no indication of results being associated with participation. Participation was lower among glioma cases than among meningioma cases. This was not related to a delayed ascertainment of glioma cases, but to the nature of the disease, with a fast deteriorating course, and the glioma patients being too sick to participate already when approached. Extra effort was made to have a rapid ascertainment for glioma cases as reflected by them being interviewed on average earlier than meningioma cases and controls. Participation did not vary by age except for a slightly lower participation among older glioma cases. This pattern was seen in all countries.

We found associations between reproductive history and glioma and meningioma risk that support the hypothesis that sex hormones may play a role in the occurrence of glioma and meningioma. The results give, however, not a totally coherent picture. The higher incidence of meningioma among women compared with men implies an increased risk associated with female hormones. The assumption therefore would be that an early menarche and a late menopause would increase risk, something we did not find. Supporting the hypothesis is our finding of an in increased meningioma risk by number of pregnancies leading to live births among younger women, which could indicate an effect of hormones on tumor growth rather than tumor initiation. For glioma, the hypothesis works in the opposite direction and an early menarche and late menopause would be assumed to be protective. We found an increased glioma risk associated with increasing age at menarche but no association with age at menopause. Increasing number of pregnancies was inversely related to glioma risk. Longer duration of breast-feeding and old age when giving birth for the fist time increased glioma risk. These findings need to be confirmed in future studies before any firm conclusions can be drawn.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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We thank all patients, controls, interviewers, and team collaborators in the study in all the participating countries as listed in Lahkola et al. (50) for their invaluable contribution to this work.

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