Risk Factors for Pituitary Tumors: A Case-control Study

Minouk J. Schoemaker and Anthony J. Swerdlow

Institute of Cancer Research, Sutton, United Kingdom

Abstract

Pituitary gland tumors are usually benign but are associated with substantial morbidity. Their etiology is largely unknown. We conducted a population-based case-control study of potential risk factors for pituitary tumors in Southeast England. Information on medical and reproductive history, female sex hormones, and cigarette smoking was collected by personal interview from 299 cases and 630 controls aged 18 to 59 years. Tumor risk was reduced in subjects reporting a past diagnosis of hay fever [odds ratio (OR), 0.7; 95% confidence interval (CI), 0.5-1.0] but not asthma or eczema. Risk was raised in women who were postmenopausal 1 year before diagnosis (OR, 3.2; 95% CI, 1.6-6.2), especially if menopause was surgically induced (OR, 6.7; 95% CI, 2.2-19.9) or occurred under age 40 years (OR, 7.5; 95% CI, 2.6-21.4). This effect remained when evaluating menopausal status 10 years before diagnosis. There was no association with parity overall, but risk was increased for first childbirth under age 20 years compared with nulliparity (OR, 3.4; 95% CI, 1.4-8.4). No significant association was observed with ever use of oral contraceptives or hormone replacement therapy, nor with cigarette smoking, past head injury, past diagnosis with epilepsy, or birth characteristics, except for an inverse association of risk with maternal age. This study suggests a raised risk of pituitary tumors in relation to surgically induced menopause, early postmenopausal age, and young age at childbirth, and possibly a reduced risk with hay fever and increasing maternal age. Reasons for these associations need further investigation, but some associations might be due to hormonal effects of an undiagnosed pituitary tumor. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1492–500)

Introduction

Pituitary tumors arise from the pituitary gland and comprise 10% to 15% of all diagnosed intracranial tumors (1, 2). They are usually adenomas, and may be hormone-secreting or nonfunctioning. Despite their predominantly benign nature, they are associated with substantial morbidity, through compression of surrounding structures and oversecretion of pituitary hormones. Hormone-secreting tumors most frequently secrete prolactin, leading to hyperprolactinemia, with resulting amenorrhoea, galactorrhea, impotence, and visual disturbances. Acromegaly may result from a pituitary tumor oversecreting growth hormone and Cushing syndrome from an adrenocorticotropin-secreting pituitary tumor. Nonfunctioning tumors produce symptoms by compressing the optic chiasm, hypothalamus, and surrounding structures (2, 3).

The etiology of pituitary tumors is largely unknown. The genetic syndromes *Multiple endocrine neoplasia 1* (*MEN1*) and *Carney complex* (*CNC*) are associated with increased susceptibility but account for a small proportion of cases (4, 5). Germline mutations in the aryl hydrocarbon receptor interacting protein (*AIP*) gene have recently been reported to account for a substantial proportion of growth hormone–secreting pituitary adenomas (6). Few studies have been conducted into other potential risk factors, and reported studies have generally been small and have largely focused on oral contraceptive use (7-13) or parity (13, 14) because of a possible causal role of estrogens, with some having reported on twinning (15), familial risks (16), or associations with other neoplasms (17). Several other factors, although not previously investigated in relation to pituitary tumors, such as a history of allergic disease and epilepsy, are of potential interest because they have been previously implicated in the etiology of other types of intracranial tumors (18).

We therefore conducted a population-based case-control study in Southeast England of potential risk factors for pituitary neoplasms, including 299 cases and 630 controls. The aim of the study was to investigate a wide range of potential risk factors including allergic disease, past diagnosis of epilepsy and other neoplasms, past head injury, birth characteristics, female reproductive history and sex hormones, and cigarette smoking.

Materials and Methods

A case-control study of pituitary tumor etiology was conducted in the Thames regions of Southeast England. It was conducted in parallel with case-control studies of several other types of intracranial tumors, according to the same study protocol and using the same questionnaire; these studies contributed data to the Interphone

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Requests for reprints: Minouk J. Schoemaker, Institute of Cancer Research, Section of Epidemiology, Sir Richard Doll Building, Sutton, SM2 5NG Surrey. Fax: +44-02087224019. E-mail: minouk@icr.ac.uk

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study, a 13-country case-control study of brain tumors in relation to cellular phone use (19). Although the core study was specifically designed to address the hypothesis of cellular phone use, we extended our local study to include pituitary tumors and additional potential risk factors, such as female reproductive factors and sex hormones, so that we were able to investigate a wider range of potential risk factors.

Eligible cases had to be diagnosed with a pituitary tumor between 1 December 2000 and 28 February 2005 and had to be ages 18 to 59 y and resident in the study region at the time of diagnosis. The choice of age range was aimed to maximize the likelihood of exposure to cellular phones, as this was the primary hypothesis of the study. A pituitary tumor was defined according to the International Classification of Diseases revision 10 (20) as topography C75.1, D35.2, or D44.3. The date of diagnosis was defined as the date of the first scan that revealed a space-occupying lesion of the pituitary gland or, if not available, the date of pathologic diagnosis. Cases were recruited primarily from the main neurosurgical centers and oncology units in the hospitals in the study region. We also ascertained cases from the Thames Cancer Registry, which covers our study region, to identify and recruit cases we failed to ascertain through the hospitals, and therefore to enable an as complete as possible population-based ascertainment. Ethical approval for the study was obtained from the Southeast Multicentre Research Ethics Committee.

Control subjects were selected, by a preset algorithm, from patients' lists at general practitioner practices in the study region. Controls were subject to the same age and residence criteria as the cases to be eligible for the study, and were excluded if they reported a past diagnosis of an intracranial tumor. GP practice lists were considered as a good source of population-based controls because ~98% of the UK population has been estimated to be registered with a GP (21). A single group of controls was recruited for the several case-control studies of intracranial tumors conducted, frequency matched on the age, sex, and health authority distributions of the total group of cases.

Ascertained cases and controls were invited by letter to participate in the study. This letter included a reply slip and a stamped envelope to return to the research team. If no reply was received after several weeks, the subject was contacted by telephone, or if that was not possible, was sent a repeat letter.

Subjects who were willing to take part in the study were interviewed face-to-face by trained research nurses. Written informed consent was obtained from all subjects. The interview was conducted using a structured computer-assisted interview using Blaise software (22), with answers being entered directly into the questionnaire program on a laptop computer. The information collected included female reproductive and hormonal factors, other factors related to medical history, and cigarette smoking. Medical history included past diagnosis of allergy, past diagnosis of epilepsy and of prior neoplasms, a history of head injury, and birth characteristics. We also collected information on cellular phone use, which is reported on elsewhere (23).

Statistical Analysis. Conditions or exposures with an onset of <1 year before diagnosis were excluded from the analysis, with the exception that use of hormonal contraceptives and treatments was included up to the date of interview because information on start and stop dates was not collected in a way that enabled us to truncate exposures up to the diagnosis date. All interviewed controls recruited for the entire set of cases were used for this analysis to increase statistical power. As controls were not individually matched to cases, we derived a reference date similar to that of the diagnosis date of the cases to truncate their exposures, based on interview year and how far back subjects were asked to recall exposures. This was done by constructing case-strata by calendar year of interview and single year interval between diagnosis and interview (''interview lag time''). Controls were randomly allocated to strata of interview lag time, proportionally to the distribution of the cases in the same calendar year, to obtain a similar distribution of lag time as in the cases. The reference dates for controls were then calculated by subtracting the mean interview lag time in cases in that stratum from the interview dates of the controls.

In the analyses, postmenopausal status was defined as having had a bilateral oophorectomy or periods having stopped at least 1 y before the reference date. True menopausal status could not be assessed for women who had had a hysterectomy without bilateral oophorectomy at an age at which they reported that they were premenopausal: this group was therefore considered separately in the analyses.

An unconditional logistic regression model was used to obtain odds ratios (OR) for risk of a pituitary tumor in relation to the risk factors investigated. All ORs were adjusted for sex, 5-y age group at the reference date, region (5 areas), interview year, and Townsend deprivation score, the latter being a socioeconomic index based on the subject's residential postcode (24). The statistical package Stata was used in all analyses (25). All P values presented are two-sided.

As exposure to ionizing radiation is a risk factor for pituitary tumors (26), we considered the effect on the results after excluding subjects who reported having had radiotherapy to the head >10 y before the reference date. We also repeated the analyses with a 5- and 10-y instead of a 1-y lag time, where appropriate, and for males and females separately.

Results

A total of 506 incident cases with pituitary tumors who satisfied the age and residence criteria were ascertained during the study period. We excluded 189 cases because of patient refusal (n = 84), no reply (n = 75), death or illness (n = 13), refusal by the treating consultant (n = 9), or other reasons (n = 8). We interviewed 318 cases, corresponding to a participation rate of 63%. After interview, however, 18 cases had to be excluded because it emerged that they had been diagnosed with a pituitary tumor before the start of the study, earlier than initially apparent from the cases notes, leading to 299 cases in the analysis (Table 1). We ascertained 1,464 potentially eligible controls, and interviewed 630 of these (43.0%). Among nonparticipants, 364 (24.9%) refused to take part and 470 (32.2%) did not reply to the letter.

Cases who participated in the study were somewhat more likely to be female compared with nonparticipating

Table 1. Characteristics of study participants in a case-control study of pituitary tumors, United Kingdom, 2001 to 2005

Characteristic	Cases (n = 299)		Controls (n = 630)	
	n	%	n	%
Sex				
Male	142	47.5	294	46.7
Female	157	52.5	336	53.3
Age at reference date (y)				
18-29	26	8.7	49	7.8
30-39	70	23.4	120	19.1
40-49	103	34.5	200	31.8
50-59	100	33.4	261	41.4
Townsend deprivation score*				
1 (most affluent)	68	22.7	190	30.2
2	62	20.7	141	22.4
3	65	21.7	140	22.2
4	47	15.7	108	17.1
5 (least affluent)	57	19.1	51	8.1
Marital status				
Single	60	20.1	94	14.9
Married/cohabiting	212	70.9	471	74.8
Separated/divorced	24	8.0	52	8.3
Widowed	3	1.0	12	1.9
Not known			1	0.2
Type of tumor				
Nonfunctioning	66	22.1		
Hormone secreting	168	56.2		
Not known	65	21.7		
Hormone secreted (if hormone secreting)				
Growth hormone	59	19.7		
Adreno-corticotropic hormone	42	14.0		
Prolactin	21	7.0		
Follicle-stimulating hormone and/or luteinizing hormone	19	6.4		
Thyroid-stimulating hormone	1	0.3		
Growth hormone and prolactin	9	3.0		
Other multihormonal	14	4.7		
Type unknown	3	1.0		

Abbreviation: PRL, prolactin; GH, growth hormone.
*Townsend score (Townsend, et al. 2008; ref. 24), a postcode-based measure of deprivation, categorized into quintiles based on 2001 census data (ref. 34).

cases (52.5% versus 47.1%; χ^2 P = 0.24), somewhat older at diagnosis (mean age, 44.7 versus 43.0 years; t test P = 0.08), and more affluent (mean Townsend score, 2.9 versus 3.5; t test $P < 0.0001$). Participating controls were significantly more likely to be female (53.3% versus 36.7%; χ^2 $P < 0.001$), older (mean age at ascertainment, 46.3 versus 42.5 years; t test $P < 0.0001$), and more affluent (mean Townsend score, 2.5 versus 2.9; t test $P < 0.0001$) than nonparticipating controls.

Among participants, similar proportions of cases and controls were female (52.5% among cases versus 53.3% among controls). Cases were on average less affluent than controls (mean Townsend score, 2.9 versus 2.5), and somewhat younger (mean age at the reference date, 44.8 versus 45.8 years), and more likely to be single (Table 1). For nearly all cases (97.7%), we were able to ascertain histologic type, all of which were adenomatous neoplasms. A total of 168 tumors (56.2%) were hormone secreting, 66 (22.1%) were nonfunctioning, and for 65 (21.7%), we were unable to obtain data. Tumors were heterogeneous in the type of hormone secreted.

Allergies. Risk of a pituitary tumor was not associated with a past diagnosis of asthma or eczema but was borderline significantly reduced with hay fever (Table 2). The OR in relation to any allergic disease was also somewhat reduced, with a suggestion of a trend of decreasing risk with increasing number of allergic conditions reported.

Tumor risk was significantly reduced in subjects who reported that they had hay fever 1 year before diagnosis [OR, 0.6; 95% confidence interval (CI), 0.4-0.9] but not in subjects whose hay fever had stopped before this (OR, 1.3; 95% CI, 0.6-2.7). There was no trend of risk with number of years the subjects had had hay fever, age at onset, or time because onset, although for the latter, risk was most strongly reduced with hay fever that started <10 years ago (OR, 0.4; 95% CI, 0.2-1.0; not in table).

Nonsignificant inverse associations were also observed for seasonal (OR, 0.4; 95% CI, 0.2-1.1) and nonseasonal (OR, 0.5; 95% CI, 0.2-1.3) allergic rhinitis and conjunctivitis, and for food allergy (OR, 0.7; 95% CI, 0.3-1.4) and contact allergy (OR, 0.7; 95% CI, 0.4-1.3; not in table).

Analyses restricted to subjects who reported hay fever and/or allergic rhinitis and conjunctivitis showed somewhat lower tumor risks in those who reported ever use of antiallergenic medication compared with those who did not (OR, 0.8; 95% CI, 0.3-2.1; not in table).

Epilepsy. Seven cases and 12 controls reported that they had ever been diagnosed with epilepsy (OR, 0.9; 95% CI, 0.3-2.7). There was no trend of risk with time since diagnosis or age at diagnosis of epilepsy and no

Table 2. Risk of a pituitary tumor in relation to past diagnosis of allergic disease in a case-control study, United Kingdom, 2001 to 2005

Factor	Cases (n = 299)		Controls (n = 630)		OR (95% CI)*	P
	n	%	n	%		
Ever diagnosis						
Asthma						
No	258	86.3	541	85.9	1.0	
Yes	41	13.7	89	14.1	0.9 (0.6-1.5)	0.78
Hay fever						
No	225	75.3	438	69.5	1.0	
Yes	74	24.8	192	30.5	0.7 (0.5-1.0)	0.06
Eczema						
No	256	85.6	533	84.6	1.0	
Yes	43	14.4	97	15.4	1.0 (0.6-1.6)	0.98
Other allergy †						
No	223	74.6	430	68.3	1.0	
Yes	76	25.4	200	31.8	0.8 (0.5-1.1)	0.13
Any of above						
No	139	46.5	262	41.6	1.0	
Yes	160	53.5	368	58.4	0.8 (0.6-1.1)	0.21
No of conditions						
1	100	33.4	205	32.5	0.9 (0.6-1.3)	0.60
2	38	12.7	90	14.3	0.8 (0.5-1.3)	0.28
≥3	22	7.4	73	11.6	0.6 (0.4-1.1)	0.13
					P_{trend} = 0.09	

*ORs obtained from unconditional logistic regression model adjusted for sex, age at reference date, region, interview year, and Townsend deprivation score.
†Seasonal or nonseasonal allergic rhinitis and conjunctivitis, food allergy, contact allergy, other types of allergy.

association of risk with use of antiepileptic medication (data not shown).

Head Injury. The OR for a pituitary tumor in relation to a history of head injury resulting in loss of consciousness and/or hospitalization was 0.9 (95% CI, 0.6-1.3), with no trend of risk with the total number of injuries or with age at first head injury (data not shown).

Birth Characteristics. Risk of a pituitary tumor was not significantly associated with any of the subjects' birth characteristics investigated, i.e., being a twin, caesarean delivery, paternal age, birth order, or crude measures of birth weight (''light'', ''normal'', ''heavy'') and gestational age (''early'', ''normal'', ''late''), except for a significant inverse trend of risk with increasing maternal age (OR per 1 year increase in maternal age: OR, 0.97; 95% CI, 0.94-1.00; P = 0.03; data not shown).

Previous Neoplasms. Sixteen cases (5.4%) and 28 controls (4.4%) reported a past diagnosis of a neoplasm at least 1 year before the reference date (OR, 1.4; 95% CI, 0.7-2.8). Pituitary tumor risk in relation to a past neoplasm was raised, but not significantly so, in females (OR, 2.0; 95% CI, 0.9-4.7) but was not raised in males (OR, 0.7; 95% CI, 0.1-3.7). Among females, 37 neoplasms were reported by 13 cases and 21 controls, with breast neoplasms being most frequently reported (OR, 2.4; 95% CI, 0.7-7.9; 6 cases, 9 controls), which was almost entirely due to benign breast neoplasms (OR, 3.2; 95% CI, 0.9-11.7; 6 cases, 6 controls). Other reported neoplasms in females included nine of the reproductive organs (four cases, five controls), five of endocrine organs (one case, four controls), and seven others of a heterogeneous nature (data not shown).

Female Reproductive Factors and Sex Hormones. Among females, a higher proportion of cases than controls (34.4% versus 29.8%) were classified as postmenopausal 1 year before the reference date, despite the fact that cases were on average 2.7 years younger than controls. Adjustment for age and other matching factors showed that tumor risk in relation to being postmenopausal was over 3-fold significantly raised (Table 3). Risk was greater for surgically induced menopause than natural menopause, and was greatest in women who entered menopause under age 40 years.

Seven women (4 cases, 3 controls) had a surgically induced menopause under age 40 years, 13 women (5 cases, 8 controls) at ages 40 to 49 years, and 1 control at age 51 years. One case underwent this procedure <2 years before being diagnosed with a pituitary tumor, whereas the remaining 8 cases underwent it 6 to 19 years prior. The hormonal behaviors of the tumors were heterogeneous: three multihormonal, two growth hormone producing, one adrenocorticotropin producing, two nonfunctioning, and one unknown. The reasons for the surgical procedures are unknown to us for the majority of patients, except that one case and one control had the procedure because of a prior reproductive cancer and one case and one control because of prolonged gynecologic problems.

There was no significant association of pituitary tumor risk with parity (Table 3) or pregnancy history (OR, 0.9; 95% CI, 0.5-1.6; not in table). Tumor risk was significantly raised among women who had their first child under age 20 years compared with nulliparous women, but there was no clear trend of risk with age at first birth or with number of children. The OR in relation to ever breastfeeding in parous women was 1.5 and was 2.1 for breastfeeding for a total of <6-month duration but was considerably lower for longer durations.

Analyses of risk in relation to use of hormonal contraception and treatments, evaluated up to the date of interview, showed that cases were somewhat less likely to ever have used oral contraceptives than controls and more likely to have been on hormone replacement therapy (HRT; Table 4). Cases were significantly more likely than controls to report HRT use for a cumulative duration of <1 year. No significant associations were observed with use of long-lasting (nonoral) hormonal contraceptives (OR, 1.4; 95% CI, 0.7-2.8), hormonal treatment for gynecologic disorders (OR, 1.3; 95% CI: 0.6-2.7), or hormonal fertility treatment (OR, 1.1; 95% CI, 0.5-2.5; not in table).

Cigarette Smoking. Tumor risk in relation to ever-regular cigarette smoking was not appreciably raised (Table 5). There was no trend of risk with total years smoked, cigarette pack-year, or age at starting smoking (not in table).

Further Analyses. One case and one control had had radiotherapy to the head at least 10 years before

Table 3. Risk of a pituitary tumor in relation to age at menarche, menopausal status, parity, and breastfeeding in a case-control study, United Kingdom, 2001 to 2005

Factor	Cases (n = 157)		Controls (n = 336)		OR (95% CI)*	P
	n	%	n	%		
Age at menarche (y)						
<12	37	23.6	77	22.9	1.0	
12-14	92	58.6	212	63.1	0.7 (0.4-1.2)	0.25
≥15	28	17.8	47	14.0	0.9 (0.4-1.8)	0.74
					P_{trend} = 0.5	
Menopause						
Menopausal status						
Premenopausal	95	60.5	209	62.2	1.0	
Postmenopausal	54	34.4	100	29.8	3.2 (1.6-6.2)	0.001
Not known due to hysterectomy †	8	5.1	23	6.9	1.6 (0.6-4.3)	0.38
Not known for other reasons			4	1.2		
Type of menopause						
Natural	43	27.4	86	25.6	2.3 (1.2-4.7)	0.02
Surgical	9	5.7	12	3.6	6.7 (2.2-19.9)	0.001
Not known	2	1.3	2	0.6		
Age at menopause (if postmenopausal, y)						
<40	16	10.7	9	2.9	7.5 (2.6-21.4)	<0.001
40-49	25	16.8	44	14.2	2.7 (1.2-6.1)	0.02
≥50	13	8.7	45	14.6	1.3 (0.5-3.6)	0.62
Not known			2	0.7	Trend (postmenopausal only) P = 0.6	
Live births						
Any						
No	41	26.1	83	24.7	1.0	
Yes	116	73.9	253	75.3	1.2 (0.7-2.1)	0.48
Age at first live birth (y)						
<20	20	12.7	16	4.8	3.4 (1.4-8.4)	0.008
20-24	42	26.8	85	25.3	1.2 (0.6-2.3)	0.62
25-29	30	19.1	92	27.4	0.9 (0.4-1.8)	0.69
30-34	11	7.0	41	12.2	0.7 (0.3-1.8)	0.52
≥35	9	5.7	14	4.2	2.1 (0.7-6.1)	0.20
Not known	4	2.6	5	1.5	Trend (parous only) P = 0.1	
No of children						
1	27	17.2	48	14.3	1.4 (0.7-2.9)	0.32
2	47	29.9	129	38.4	1.0 (0.5-1.9)	0.96
3	26	16.6	49	14.6	1.6 (0.8-3.4)	0.22
≥4	16	10.2	27	8.0	1.2 (0.5-2.9)	0.67
					Trend (all subjects) P = 0.4	
					Trend (parous only) P = 0.6	
Breastfeeding (parous only)						
Ever						
No	35	22.2	94	28.0	1.0	
Yes	79	50.3	150	44.6	1.5 (0.8-2.7)	0.17
Not known	2	1.3	9	2.7		
Lifetime months breastfeeding						
1-6	28	17.8	40	11.9	2.1 (1.0-4.5)	0.06
7-11	19	12.1	56	16.7	1.2 (0.6-2.8)	0.60
12-17	11	7.0	21	6.3	1.6 (0.6-4.2)	0.39
≥18	21	13.4	30	8.9	1.3 (0.6-3.2)	0.51
Not known			3	0.9	Trend (all subjects) P = 0.9	
					Trend (ever breastfed only) P = 0.2	

*ORs obtained from unconditional logistic regression model adjusted for sex, age at reference date, region, interview year, and Townsend deprivation score.

†Menopausal status could not be assessed because women had a premenopausal hysterectomy without bilateral oophorectomy.

Table 4. Risk of a pituitary tumor in relation to hormonal contraceptive use and treatment, evaluated up to the date of interview in a case-control study, United Kingdom, 2001 to 2005

Factor	Cases (n = 157)		Controls (n = 336)		OR (95% CI)*	P
	n	%	n	%		
Oral contraceptive use						
Ever						
No	35	22.3	53	15.8	1.0	
Yes	122	77.7	283	84.2	0.8 (0.4-1.4)	0.38
Duration of oral contraceptive use (y)						
<1	15	9.6	25	7.4	1.6 (0.7-4.1)	0.30
1-4	36	22.9	82	24.4	0.8 (0.4-1.7)	0.64
5-9	28	17.8	84	25.0	0.5 (0.2-1.1)	0.07
≥10	42	26.8	90	26.8	0.7 (0.4-1.5)	0.41
Not known	1	0.6	2	0.6	Trend (all subjects) P = 0.2 Trend (ever users only) P = 0.3	
HRT						
Ever						
No	116	73.9	234	69.6	1.0	0.16
Yes	41	26.1	102	30.4	1.5 (0.8-2.6)	
Duration of HRT use (y)						
<1	13	8.3	17	5.1	3.3 (1.3-8.6)	0.01
1-4	13	8.3	28	8.3	1.5 (0.6-3.3)	0.37
5-9	9	5.7	37	11.0	0.9 (0.4-2.3)	0.85
≥10	6	3.8	20	6.0	1.1 (0.4-3.4)	0.87
Not known					Trend (all subjects) P = 0.6 Trend (ever use only) P = 0.4	

*ORs obtained from unconditional logistic regression model adjusted for age at reference date, region, interview year, and Townsend deprivation score.

the reference date, which is unlikely to have affected the results. In analyses excluding the first 5 or 10 years before diagnosis, risks remained significantly raised in relation to surgically induced menopause, young age at menopause (<40 years), and young age at first childbirth, but risks for natural menopause were no longer raised. The OR for hay fever was nearly identical to that in the main analyses after excluding the first 5 years before diagnosis but was somewhat closer to 1.0 after excluding the first 10 years (OR, 0.8; 95% CI, 0.6-1.2). Associations with allergy were particularly due to such an association among females, e.g., for hay fever, ORs were 0.5 (95% CI, 0.3-0.9) for females and 0.9 (95% CI, 0.6-1.5) for males, but there was no statistically significant heterogeneity in effect by sex (data not shown). ORs for cigarette smoking were similar between males and females.

Discussion

In our study, the first to explore a wide range of potential risk factors for pituitary neoplasms, we observed positive associations of pituitary adenoma risk with menopausal status and young age at first birth among females and inverse associations with maternal age at the proband's birth and past diagnosis of hay fever. No significant associations were observed with cigarette smoking, head trauma, past diagnosis of epilepsy, or past diagnosis of a neoplasm, although for the latter,

Table 5. Risk of a pituitary tumor in relation to ever regular cigarette smoking in a case-control study, United Kingdom, 2001 to 2005

Factor	Cases (n = 299)		Controls (n = 630)		OR (95% CI)*	P
	n	%	n	%		
Regular smoking [†]						
Ever						
No	154	51.5	338	53.7	1.0	
Yes	145	48.5	292	46.4	1.2 (0.9-1.7)	0.26
Total cumulative years smoked						
<10	35	11.7	81	12.9	1.1 (0.7-1.9)	0.62
10-19	56	18.7	98	15.6	1.3 (0.8-2.1)	0.22
20-29	29	9.7	55	8.7	1.2 (0.7-2.1)	0.51
≥30	25	8.4	58	9.2	1.1 (0.6-2.0)	0.58
					P_{trend} = 0.5	

*ORs obtained from unconditional logistic regression model adjusted for sex, age at reference date, region, interview year and Townsend deprivation score.
[†]At least 1 cigarette per day for 6 mo or more.

there was a suggestion of an association with benign breast tumors.

Tumor risk was significantly raised in women who were postmenopausal 1 year before diagnosis, with risks being greatest in those whose menopause had been surgically induced. All except 1 of the 9 cases who underwent this procedure did so >6 years before diagnosis with a pituitary tumor, making it less likely, although not impossible, that the conditions that led to the decision to undertake the procedure were due to an occult pituitary tumor. It is possible that oophorectomy itself, or the gynecologic conditions leading up to the procedure, are associated with pituitary tumor risk. The raised risk in relation to a natural (i.e., nonsurgically induced) menopause in the main analysis was not observed in subanalyses that excluded the first 5 years before diagnosis, suggesting that this association may have been due to tumor-induced amenorrhoea (3).

Tumor risk was not significantly related to pregnancy history, parity, or breastfeeding in our study, except that risk was significantly raised in women who had their first child under age 20 years, a finding possibly due to chance or to hormonal effects of pregnancy at young ages. Two previous studies have investigated pituitary tumor risk in relation to parity (13, 14), both of which reported a markedly reduced risk in parous women, contrary to the hypothesis that pregnancy-related pituitary hyperplasia might be expected to increase the risk of pituitary adenoma. Such findings might be due to the presence of subclinical pituitary tumors causing suboptimal fertility before formal diagnosis in cases. The largest study, based on record-linkage of 350 pituitary tumor cases in Sweden, reported an OR of 0.55 (95% CI, 0.40-0.77) for 1 child compared with none (14). Parity was evaluated as at the date of diagnosis, unlike in our study in which the first year before diagnosis was excluded, but this seems unlikely to account for the substantial difference in results compared with our study.

The potential role of oral contraceptive use in pituitary tumorigenesis is of interest because estrogen is known to stimulate growth of lactotrophs, pituitary cells that produce prolactin, and studies of animals treated with estrogens have reported increased rates of pituitary tumors (2, 27-29). It has been suggested therefore, that prior oral contraceptive use could increase risk of pituitary tumors (27). Our study did not show an association of risk with past use of oral contraceptives; however, nor did earlier epidemiologic studies provide consistent evidence for such an effect (7-13), including a study of 212 cases of prolactinoma (13). With regard to HRT, we observed that cases were thrice more likely than controls to report HRT use for <1 year, which is likely to be due to cases starting HRT as a consequence of diagnosis of or surgery for a pituitary tumor (29). The lack of information on start and end dates of HRT use is a limitation of our study.

Tumor risk was borderline significantly reduced in subjects previously diagnosed with hay fever, and nonsignificantly reduced with several other allergic conditions. Past epidemiologic studies have consistently reported reduced risks of glioma in relation to atopic disease (30), and although causality has not been established, the association might be due to raised tumor immunosurveillance in subjects with allergy (31). Such an effect might also be present for pituitary tumors, although our findings could potentially also be explained by other factors, including selection bias among controls, bias in recall of allergy, and reverse causality. For the latter, the presence of an occult tumor might have affected immunologic status and explain why pituitary tumor risks were mostly strongly reduced in current sufferers from hay fever and in those whose hay fever started <10 years before diagnosis. Subjects with allergy who reported ever use of antiallergenic medication showed a somewhat reduced tumor risk, which could be due to chance, a protective effect of the medication per se, or treatment could be an indicator of more severe allergy.

We observed no significant associations of pituitary tumor risk with cigarette smoking, history of head trauma, past diagnosis of epilepsy, or past diagnosis of other neoplasms. Among females, risk was nonsignificantly increased in women who had had a previous neoplasm, which was mainly due to benign breast neoplasms, based on small numbers. We are not aware of previous studies of multiple neoplasms that have reported on pituitary tumors, the only exception being the Swedish Family-Cancer database study (17), which reported no raised risk of breast cancer *after* pituitary tumor diagnosis. No data on pituitary tumor risk after breast cancer were presented, but it did report a raised pituitary tumor risk after diagnosis of thyroid cancer, parathyroid adenoma, adrenal tumors, and colorectal cancer; these associations may be due to involvement of *MEN1*. However, interestingly, excess risks of pituitary tumors were observed in offspring of mothers with breast cancer, and pituitary tumors and breast cancers were found to be associated in sibling pairs (16). With regard to birth characteristics, we observed a significant decreasing trend in risk with increasing maternal age. Reasons for this are unclear and this association needs further investigation in other studies. We did not observe a positive association of risk with twinning, unlike a previous study (15), but the number of twins in our study was small.

Only 43% of mailed controls took part in our study, largely due to lack of willingness of people to take part in unpaid medical studies and high residential mobility in the study region. The true participation rate is likely to have been appreciably higher than this, however, because some people will not have received the invitation letter at all, for example, because they moved address. From additional data on probable addresses, we calculate that our true control participation rate might be up to 63%, depending on the proportion of subjects who did not reply because they had actually moved. Our low participation rate is a possible source of bias, but it is difficult to assess the extent to which this might have affected our results. Among controls, participating subjects were more likely to be female, older, and more affluent than nonparticipating subjects. This was, however, also observed for cases, which could have compensated for the effect of selective participation of controls. Participating controls were still older and more affluent than participating cases, but all analyses were adjusted for age and Townsend deprivation score; the possibility of residual confounding by socioeconomic factors remains, however. The study was presented to prospective participants as a study of modern life-style

factors and family on health, without emphasis on any particular factor, which should, in theory, have reduced the potential for recall bias.

There are methodologic problems associated with studying risk factors for pituitary tumors, in particular that latency time is thought to be long so that associations with apparently prior risk factors might be a consequence of the past presence of a tumor in the preclinical stage, and that the different types of pituitary tumor (2) might have different etiologies. A prevalence study in Belgium showed that patients had on average suffered symptoms attributable to a pituitary tumor for 45.3 months before formal diagnosis (32). We therefore repeated the main analyses after excluding the first 5 and 10 years before diagnosis. Additionally, it is thought, from autopsy and radiology studies, that small asymptomatic pituitary tumors are very common but frequently remain undiagnosed (33). Our study is necessarily of pituitary tumors that have come to clinical attention. We only included cases ages 18 to 59 years, and given that the peak incidence of pituitary tumors is beyond age 60 years (16), our study is of early-onset pituitary tumors, which might have affected the generalizability of our findings. The distribution of tumors by hormone secreted in our study is different from that reported by others (2, 32), with a considerable lower proportion of prolactinomas, but our data were based on a subset of cases participating in the study and information on hormone secretion was not known for a fifth of cases.

In conclusion, this study of potential risk factors for early-onset pituitary tumors shows an increased risk with surgically induced menopause, young postmenopausal age, and young age at first childbirth, and possibly a reduced risk with past diagnosis of hay fever and maternal age at the proband's birth. This is the first study reporting on such associations and future studies need to include later-onset cases to determine whether these risk factors are restricted to those of early onset.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Minouk J. Schoemaker and Anthony J. Swerdlow

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