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NON-COMMUNICABLE DISEASE RISK FACTORS

Mobile phone use and risk of brain neoplasms and other cancers: prospective study

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Background Results from some retrospective studies suggest a possible increased risk of glioma and acoustic neuroma in users of mobile phones.

Methods The relation between mobile phone use and incidence of intracranial central nervous system (CNS) tumours and other cancers was examined in 791 710 middle-aged women in a UK prospective cohort, the Million Women Study. Cox regression models were used to estimate adjusted relative risks (RRs) and 95% confidence intervals (CIs). Women reported mobile phone use in 1999 to 2005 and again in 2009.

Results During 7 years' follow-up, 51 680 incident invasive cancers and 1 261 incident intracranial CNS tumours occurred. Risk among ever vs never users of mobile phones was not increased for all intracranial CNS tumours (RR = 1.01, 95% CI = 0.90–1.14, $P = 0.82$), for specified CNS tumour types nor for cancer at 18 other specified sites. For long-term users compared with never users, there was no appreciable association for glioma (10+ years: RR = 0.78, 95% CI = 0.55–1.10, $P = 0.16$) or meningioma (10+ years: RR = 1.10, 95% CI = 0.66–1.84, $P = 0.71$). For acoustic neuroma, there was an increase in risk with long term use vs never use (10+ years: RR = 2.46, 95% CI = 1.07–5.64, $P = 0.03$), the risk increasing with duration of use (trend among users, $P = 0.03$).

Conclusions In this large prospective study, mobile phone use was not associated with increased incidence of glioma, meningioma or non-CNS cancers.

Keywords Acoustic neuroma, glioma, meningioma, cellular phone, neoplasms, prospective studies

Introduction

A Working Group within the International Agency for Research on Cancer (IARC) monograph programme on the evaluation of carcinogenic risks to humans has recently classified radio frequency electromagnetic fields, such as those emitted by mobile telephones, as 'possibly carcinogenic to humans' (Group 2B), based on limited evidence from epidemiological studies for an association between use of mobile phones and the risk of glioma and acoustic neuroma (but not of meningioma).[1] The only certain biological effect of the

non-ionizing radio-frequency radiation emitted by mobile phones is a small rise in tissue temperature of the brain and adjacent organs,[2] and there is only weak evidence for related potential mechanisms of carcinogenesis.[1]

The majority of epidemiological studies reviewed by IARC compared retrospectively reported use of mobile phones by patients with a diagnosed brain tumour with use reported by people who did not have a brain tumour. In some instances, proxy respondents, often relatives of the patient, were interviewed when those with brain tumours had died, or were too ill to respond. Recall of past mobile phone use could potentially differ between those with and without brain tumours, particularly if the reporting of past use was not by the patients themselves.[3] The only published study where information on mobile phone use was recorded prospectively, i.e. before the diagnosis of a brain tumour, reported no increase in the risk of any tumour of the brain or of other cancers.[4,5] Where information on mobile phone use is collected prospectively, recall of use should not differ between those who subsequently develop brain tumours and those who do not (except, perhaps, if a brain tumour was diagnosed soon after data collection, and early symptoms of the disease affected the person's recall of past events).

We report here on the relation between prospectively recorded information on use of mobile phones and the incidence of intracranial central nervous system (CNS) tumours and of other cancers (both overall and at 18 separate sites) in a large UK cohort of middle-aged women. For comparison, we also report results for incidence of hospitalization for stroke and ischaemic heart disease.

Materials and Methods

Study design, data collection and follow-up

During the period 1996–2001, 1.3 million middle-aged women were recruited through the UK National Health Service (NHS) Breast Screening Programme into the Million Women Study (see Supplementary data at *IJE* online), completing a postal questionnaire about sociodemographic, medical and lifestyle factors. The study population is resurveyed approximately every 3–4 years. Full details of the study design and methods are described elsewhere[6,7] and all questionnaires can be viewed at http://www.millionwomenstudy.org. Questions on mobile phone use were asked in 1999–2005, and again in 2009.

All study participants have a unique NHS number, and are followed via record linkage (using this number and other personal details) to the NHS Central Register. Cancer registrations (including non-invasive tumours of the CNS, and those of uncertain behaviour) and deaths are routinely notified to the study investigators; this information includes the date of each such event, with tumour site and morphology coded using the 10th revision of the International Classification of Diseases (ICD-10),[8] and the third edition of the International Classification of diseases for Oncology (ICD-O).[9]

Information on incident vascular disease during follow-up was obtained through linkage to Hospital Episodes Statistics (HES) in England and to Scottish Morbidity Records (SMR); these agencies provided dates and ICD-10 diagnosis codes for inpatient and day-patient hospital admissions.

All study participants gave written consent to taking part in the study, and ethical approval was provided by the Oxford and Anglia Multi-Centre Research Ethics Committee. Access to hospital admissions data was approved by the Information Centre for Health and Social Care (England) and the Information Services Division (Scotland).

Exposure variables

Women in the study have been asked twice about mobile phone use. In a survey conducted between 1999 and 2005 (to which about 65% of women recruited in 1996–2001 replied), women were asked: 'About how often do you use a mobile phone?', and given three options to respond: 'never', 'less than once a day', 'every day'; and 'For how long have you used one?' (participants were asked to provide total years of use). The responses to these questions provided baseline exposure data for analyses. In 2009, study participants were asked 'How much do you talk on a mobile phone?' (average minutes per week) and 'How long have you used a mobile phone?' (in years). This information is currently available for a random sample of 31 110 women who had also responded to the questions on mobile phone use at baseline, and although it was not used to define exposure status for analyses, it allowed assessment of the repeatability of use of mobile phones reported earlier. Of the women who reported at baseline that they had used a mobile phone, 77% of those reporting ever use (13 437/17 647) and 92% of those reporting daily use (1702/1852) also reported use for at least 1 minute per week at follow up, an average of 8.8 years later. In women reporting use at both surveys, duration of use reported at the later survey was consistent, on average, with that estimated to have accrued by that time on the basis of duration reported at baseline, assuming continued use between surveys. Approximately half (49%) of those who reported no phone use at baseline reported using a mobile phone in 2009.

Outcomes

The main outcomes examined here are registered cancers or non-invasive tumours occurring after the date that the baseline questionnaire was completed. Results are reported for incident intracranial tumours of the CNS: ICD-10 C70, C71, C72.1-5, C75.1-3, D32.0, D33.0-3, D35.2-4, D42.0, D43.0-3 and D44.3-5; and where possible, CNS tumours were further classed

by site and morphology as glioma (ICD-O 9380-9481), meningioma (ICD-O 9530-9539), pituitary tumours (C75.1, D35.2, and D44.3) and acoustic neuroma (D33.3, ICD-O 9560). Results are also reported for all invasive cancer (C00-C97, excluding non-melanoma skin cancer C44), and separately for 18 invasive cancer sites, 16 of which had accrued over 500 incident cases during follow-up and 2 others (eye and thyroid) for comparison with reports by others. The 18 cancer sites were defined as follows: 'other head and neck' (ICD-10 C00-14, C30-32, i.e. excluding CNS, eye and thyroid), oesophagus (C15), stomach (C16), colon (C18), rectum (C19-20), pancreas (C25), lung (C34), melanoma (C43), breast (C50), endometrium (C54), ovary (C56), kidney (C64), bladder (C67), eye (C69), thyroid (C73), non-Hodgkin lymphoma (C82-85), myeloma (C90) and leukaemia (C91-95).

Incident vascular disease endpoints were defined as first hospital admission with a primary diagnosis of stroke (ICD-10 I60-69) or ischaemic heart disease (ICD-10 I20-25).

Statistical analyses

Potentially eligible for these analyses were 866 525 women who responded to the study survey conducted between 1999 and 2005. Of these, 14 387 were excluded because they completed a version of the survey which did not include the question on mobile phone use, and 11 981 because they did not answer the question asked on mobile phone use. Analyses also excluded 48 531 women with a CNS tumour or any other invasive cancer [other than non-melanoma skin cancer (C44)] registered before baseline, and 6 women who reported having the inherited disorder neurofibromatosis (Q85.0) (which is associated with a high risk of neurological tumours).

Analyses for vascular disease additionally excluded women with a history of vascular disease (diagnosis of and/or treatment for heart disease or for stroke before baseline, either self-reported or identified from hospital admission data).

Cox regression models (taking attained age as the underlying time variable) were used to obtain adjusted relative risks (RRs) and 95% confidence intervals (CIs) for each of the endpoints of interest in relation to mobile phone use. Duration of use of a mobile phone was treated as a time-dependent variable, incrementing duration for each year of follow-up.

Eligible women contributed woman-years from the date they answered the baseline questions about mobile phone use until the date of diagnosis with the tumour or disease of interest, date of death or the end of follow-up, whichever was earliest. In analyses of cancer and CNS tumour outcomes, censoring was done at first cancer or CNS tumour diagnosis at any site: for stroke and ischaemic heart disease censoring was done at first diagnosis of either condition. The last date of follow-up for analyses of tumour incidence was 31 December 2009 for all 10 regions (corresponding to 10 cancer registries), except for the North West (Mersey) region and Scotland, where it was 31 December 2008 (as registrations were incomplete after that date). For vascular disease incidence, hospital admissions data were available in England until 31 March 2008 and in Scotland until 31 December 2008, with follow-up ending on these dates.

All analyses were stratified by quintiles of socioeconomic status (based on the Townsend deprivation index[10]), geographical region of residence (10 regions corresponding to the areas covered by the cancer registries) and age at baseline (<53, 53–55, 56-58, . . . , 78–80, 80+ years). Analyses were additionally adjusted for height (<160, 160–164.9, ⩾165 cm), body mass index (<25, 25–29.9, ⩾30 kg/m^2), smoking (never, past, current 1–14 cigarettes per day, current ⩾15 cigarettes per day), alcohol intake (none, <10, ⩾10 g per day), duration of strenuous exercise (<0.5 h, 0.5–1 h, ⩾1 h per week) and use of menopausal hormone therapy (never, past, current). For each adjustment and stratification variable, missing values were assigned to a separate category. For analyses of CNS tumours, sensitivity analyses were carried out excluding the first 3 years of follow-up (because pre-clinical disease may affect reporting of mobile phone use, or may cause women to change their mobile phone use) and, separately, excluding women who completed the baseline questionnaire in 1999 or 2000, because the prevalence of use of mobile phones increased rapidly over the next few years; non-users who completed the baseline questionnaire in 1999–2000 were more likely than non-users reporting in 2001–05 to have started to use a mobile phone over the follow-up period to 2009.

Where summary estimates are given combining our results with those from the Danish prospective study of mobile phone use,[4,5,11] study-specific results were combined using the method of inverse variance least squares.

National trends in the incidence of acoustic neuroma (ICD-10 code D33.3) in England were examined for the years from 1998 to 2008 by calculating annual age-standardized incidence rates per 100 000 men and women aged 20–79 years, using data on tumour incidence and population estimates from the Office for National Statistics.[12] All analyses were performed using Stata version 12.0.

Results

Baseline data were collected between 1999 and 2005, and during that period reported mobile phone use increased rapidly. The proportion of study respondents who reported at baseline that they had used a mobile phone rose from 34% of those completing the questionnaire in 1999 to 79% of those completing the questionnaire in 2005, and the proportion reporting

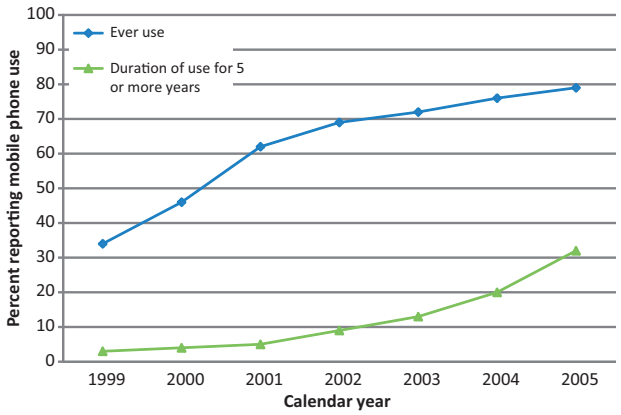

Figure 1 Reported use of mobile phones by calendar year

use for a duration of 5 or more years rose from 3% in 1999 to 32% in 2005 (Figure 1).

In total, 791 710 women with a mean age at baseline of 59.5 years (standard deviation 4.9) were included in analyses of tumour incidence. During an average of 7 years' follow-up, 51 680 incident invasive cancers and 562 incident non-invasive intracranial CNS tumours occurred; neoplasms were diagnosed on average 4.2 years after baseline report of mobile phone use. Table 1 shows the characteristics of the study population, woman-years of follow-up, average years of follow-up per woman and the number of women with intracranial CNS tumours and incident cancer according to never and ever use of a mobile phone as reported at baseline for these analyses. Table 1 also includes details of diagnoses for the 16 665 women who were admitted to hospital with stroke or ischaemic heart disease during follow-up. Mobile phone users were slightly younger, lived in more affluent areas and were more likely to do strenuous exercise, to be a current user of menopausal hormone therapy and to have taken oral contraceptives than never users of a mobile phone; they also drank more alcohol on average but were less likely to be current smokers than never users.

Intracranial CNS tumours

During follow-up, 1261 intracranial CNS tumours were reported, including 571 gliomas, 251 meningiomas, 110 pituitary tumours and 96 acoustic neuromas (the remaining 233 tumours were predominantly of unspecified type). Table 2 shows relative risks for incident intracranial CNS tumours and other cancers by ever use, daily use and duration of use of a mobile phone. The relative risk for ever use of a mobile phone for incidence of all intracranial CNS tumours taken together was 1.01, 95% CI 0.90–1.14, $P=0.82$. For specific CNS tumour types, relative risks were 0.91, 0.76–1.08, $P=0.29$; 1.05, 0.81–1.38, $P=0.70$; 1.52, 0.99–2.33, $P=0.06$; and 1.44, 0.91–2.28, $P=0.12$ for glioma, meningioma, pituitary tumours and acoustic neuroma, respectively.

Further details of the relationship between use of mobile phones and incidence of intracranial CNS tumours are shown in Table 3. Relative risks did not vary much between less than daily and daily users, for all CNS tumours taken together or for each CNS tumour type separately. Duration of use of a mobile phone for 5 or more years was associated with an increased risk of acoustic neuroma (RR for 5+ years of use *vs*. never use, 1.88, 95% CI 1.14–3.11, $P=0.01$; test for trend across categories <5, 5–9 and 10+ years of use, $P=0.03$). For pituitary tumours, the RR was increased in short-term mobile phone users with duration less than 5 years (RR = 2.31, 95% CI 1.31–4.06, $P=0.004$) but there was no evidence for a trend in risk with increasing duration of use ($P=0.23$). Excluding the first 3 years of follow-up, or excluding women who answered questions about their use of mobile phones in 1999/2000, did not materially change the findings (Table 3).

National incidence data showed no overall increase in the incidence of acoustic neuroma (ICD-10 D33.3) in either men or women at ages 20–79 years in England from 1998 to 2008 (Figure 2). Trends were similar in men and women, but confidence intervals were wide, as in each year there were only about 160 acoustic neuromas registered in men and 170 in women.

Other cancers

Risk of all invasive cancers combined was slightly reduced in mobile phone users compared with never users: ever vs never use, RR = 0.97, 95% CI 0.95–0.99, $P<0.001$). No significant associations were seen between mobile phone use and risk of cancers of the eye and thyroid, or of other head and neck cancers (Table 2). Nor was ever use of a mobile phone significantly associated with increased risk of invasive cancer at the 15 other sites examined. A significantly reduced risk was found for lung cancer in ever vs never users (RR 0.89, 95% CI 0.84–0.95, $P=0.001$).

Vascular disease

During follow-up, 4073 women had a first hospital admission for stroke and 12 592 had a first admission for ischaemic heart disease. As shown in Table 2, ever use of a mobile phone was associated with a reduced risk of stroke (RR for ever vs never use, 0.88, 95% CI 0.82–0.94, $P<0.001$), but not with risk of admission for ischaemic heart disease (RR 1.04, 95% CI 1.00–1.08, $P=0.06$).

Discussion

In this large prospective study of middle-aged UK women, use of mobile phones was not associated

Table 1 Characteristics of the study population by reported mobile phone use at baseline, and details of follow-up

	Mobile phone use	
	Never ($n = 294\,484$)	Ever ($n = 497\,226$)
Characteristics at baseline		
Mean age, years (SD)	60.3 (5.1)	59.0 (4.8)
Socioeconomic group (% in upper third)	29.6	35.7
Mean height, cm (SD)	162.0 (6.7)	162.4 (6.6)
Mean body mass index, kg/m^2 (SD)	26.0 (4.6)	26.2 (4.6)
Strenuous physical activity >one h per week (%)	52.4	58.1
Alcohol intake, $\geqslant$70 g/week (%)	21.3	29.6
Current smoker (%)	14.4	11.0
Current use of hormone replacement therapy (%)	25.7	29.3
Ever used oral contraceptives (%)	53.3	65.5
Ever had a full term pregnancy (%)	87.4	89.6
Follow-up for cancer		
Women-years of follow-up (millions)	2.3	3.5
Average years of follow-up per woman	7.7	7.1
Incident cancers (n)	21 549	30 131
Incident intracranial central nervous system tumours (n)	507	754
Follow-up for vascular disease[a]		
Women-years of follow-up (millions)	1.7	2.6
Average years of follow-up per woman	6.2	5.7
Incident stroke (n)	1993	2080
Incident ischaemic heart disease (n)	5401	7191

[a]Shorter follow-up time for vascular disease than for cancer (see text).

with an increased risk of glioma, meningioma, total cancer or cancer at 18 other specific sites. We found an increased risk of acoustic neuroma in women who had used a mobile phone for 5 years or longer, with risk increasing with increasing duration of exposure.

Possible carcinogenic effects of non-ionizing radiofrequency electromagnetic fields from handheld mobile phones have been of concern for many years, with their widespread and rapidly increasing use since the late 1990s.[13] Based on estimates of site-specific radiofrequency field dose,[14] interest has focused on risk of tumours of the head and neck, and in particular on those of the brain and cranial nerves, including glioma, meningioma and acoustic neuroma. It has also been suggested that there may be an increase in risk of leukaemia,[15,16] through exposure of bone marrow, and of malignant melanoma.[17]

In May 2011, an IARC Working Group concluded that there is 'limited evidence in humans' for the carcinogenicity of radiofrequency electromagnetic fields, based on associations between glioma and acoustic neuroma and exposure to these fields from wireless phones.[1] For meningioma and for non-CNS cancers, the IARC Working Group found the available evidence to be 'insufficient to reach a conclusion on the potential association with mobile phone use'. The epidemiological evidence, which has been extensively reviewed,[1,18–25] came largely from retrospective case-control studies, notably the INTERPHONE multicentre study[26-28] and studies from the Hardell group in Sweden.[29-31] Potential limitations of studies that collect exposure information retrospectively are well known, and are particularly pertinent for brain tumours, which may impair cognitive functioning and are often rapidly fatal. Some studies used proxy respondents to report the patient's past exposure. The INTERPHONE study of glioma risk, for example, used proxy reports of mobile phone use for 13% of cases.[26] It is not clear how proxies would affect accuracy of exposure information; the Hardell group reported similar results for living (no proxies)[32] and dead (100% proxies)[33] cases of malignant brain tumours.

Table 2 Relative risks (RRs) and 95% confidence intervals (CIs) for various outcomes in mobile phone users compared with never users

Outcome		Ever use of a mobile phone		Daily use of a mobile phone		Duration of use 10+ years	
	Total cases	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)
Neoplasms (ICD-10 codes)							
All invasive neoplasms (C00-97)	51 680	30 131	0.97 (0.95-0.99)	3684	0.95 (0.91-0.98)	4120	0.97 (0.93-1.00)
Head and neck neoplasms							
Intracranial central nervous system tumours[a]							
All	1261	754	1.01 (0.90-1.14)	90	1.00 (0.80-1.26)	103	1.02 (0.81-1.27)
Glioma (ICD-O 9380-9481)	571	334	0.91 (0.76-1.08)	36	0.80 (0.56-1.14)	40	0.78 (0.55-1.10)
Meningioma (ICD-O 9530-9539)	251	149	1.05 (0.81-1.38)	19	1.11 (0.67-1.85)	20	1.10 (0.66-1.84)
Pituitary (ICD-10 C75.1, D35.2, D44.3)	110	77	1.52 (0.99-2.33)	9	1.45 (0.68-3.10)	11	1.61 (0.78-3.35)
Acoustic neuroma (ICD-10 D33.3, ICD-O 9560)	96	67	1.44 (0.91-2.28)	8	1.37 (0.61-3.07)	8	2.46 (1.07-5.64)
Other/unspecified	233	127	0.93 (0.71-1.21)	18	1.19 (0.71-1.99)	24	1.03 (0.65-1.65)
Other head and neck							
Eye (C69)	87	52	1.01 (0.64-1.60)	5	0.75 (0.29-1.97)	5	0.82 (0.31-2.19)
Thyroid (C73)	345	216	1.07 (0.85-1.35)	21	0.85 (0.53-1.37)	32	1.06 (0.71-1.61)
Other (C00-14, 30-32)	719	417	0.98 (0.84-1.15)	46	0.79 (0.58-1.09)	57	1.00 (0.74-1.35)
Other neoplasms							
Oesophagus (C15)	666	355	0.90 (0.77-1.06)	30	0.61 (0.42-0.90)	52	1.02 (0.75-1.39)
Stomach (C16)	566	290	0.84 (0.70-1.00)	32	0.75 (0.52-1.10)	40	0.96 (0.68-1.36)
Colon (C18)	3803	2152	0.95 (0.89-1.02)	236	0.93 (0.81-1.07)	323	0.95 (0.84-1.08)
Rectum (C19-20)	1826	1056	0.95 (0.86-1.05)	124	0.94 (0.77-1.14)	146	0.92 (0.76-1.10)
Pancreas (C25)	1240	713	1.09 (0.96-1.22)	70	0.94 (0.72-1.21)	103	1.04 (0.83-1.30)
Lung (C34)	4162	2148	0.89 (0.84-0.95)	342	0.99 (0.88-1.11)	293	0.88 (0.78-1.00)
Melanoma (C43)	2116	1336	1.06 (0.96-1.16)	160	1.06 (0.89-1.26)	191	1.09 (0.92-1.29)
Breast (C50)	19 828	12 069	0.99 (0.96-1.02)	1514	0.97 (0.92-1.03)	1608	1.02 (0.96-1.08)
Endometrium (C54)[b]	3313	1924	0.97 (0.90-1.05)	219	0.92 (0.79-1.06)	234	0.86 (0.74-0.99)
Ovary (C56)[b]	2587	1503	0.97 (0.90-1.06)	157	0.85 (0.72-1.01)	199	0.97 (0.83-1.14)
Kidney (C64)	979	584	1.05 (0.92-1.20)	83	1.19 (0.93-1.52)	92	1.16 (0.91-1.48)
Bladder (C67)	730	394	0.90 (0.77-1.05)	42	0.79 (0.57-1.10)	65	1.10 (0.83-1.46)
Non-Hodgkin lymphoma (C82-85)	2058	1184	0.97 (0.88-1.06)	134	0.94 (0.78-1.13)	176	0.99 (0.83-1.17)
Multiple myeloma (C90)	742	427	0.98 (0.84-1.14)	50	1.01 (0.74-1.37)	59	0.87 (0.65-1.17)
Leukaemia (C91-95)	860	478	0.91 (0.79-1.05)	53	0.88 (0.66-1.19)	67	0.92 (0.70-1.21)
Vascular Disease (ICD-10 codes)							
Stroke (I60-69)	4073	2080	0.88 (0.82-0.94)	263	0.94 (0.83-1.07)	137	0.84 (0.70-1.00)
Ischaemic heart disease (I20-25)	12 592	7191	1.04 (1.00-1.08)	1055	1.25 (1.17-1.34)	477	1.01 (0.92-1.11)

[a]ICD-10 codes C70, C71, C72.1-5, C75.1-3, D32.0, D33.0-3, D35.2-4, D42.0, D43.0-3, D44.3-5.
[b]Women who have reported having had hysterectomy or bilateral oophorectomy were excluded from the analyses, as appropriate.

Consistent with the findings from the only other study with prospective recording of exposure,[5] we found no increase in the risk of glioma in mobile phone users. Combining results from the two prospective studies gives a RR of 0.98 (95% CI 0.83–1.15, $P = 0.76$) for 10 or more years of use of a mobile phone, inconsistent with the findings from the Hardell group (RR 2.5, 95% CI 1.8–3.3 in mobile phone users of more than 10 years).[31] An increased risk for glioma (RR 1.40, 95% CI 1.03–1.89) in INTERPHONE was seen only in people with the highest decile of reported call time; the lack of a dose-response relationship and the likelihood of recall bias have meant that the authors[27] and others[19]

Table 3 Relative risks (RRs) and 95% confidence intervals (CIs) for incident intracranial central nervous system (CNS) tumours and for specified glioma, meningioma, pituitary tumours and acoustic neuroma in relation to mobile phone use

	All intracranial CNS tumours		Glioma		Meningioma		Pituitary tumours		Acoustic neuroma	
Mobile phone use	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)	*n* cases	RR (95% CI)
All women										
Never	507	Ref	237	Ref	102	Ref	33	Ref	29	Ref
Ever	754	1.01 (0.90-1.14)	334	0.91 (0.76-1.08)	149	1.05 (0.81-1.38)	77	1.52 (0.99-2.33)	67	1.44 (0.91-2.28)
Frequency of use										
<Daily use	664	1.02 (0.90-1.15)	298	0.92 (0.77-1.10)	130	1.05 (0.80-1.37)	68	1.53 (0.99-2.36)	59	1.45 (0.91-2.31)
Daily use	90	1.00 (0.80-1.26)	36	0.80 (0.56-1.14)	19	1.11 (0.67-1.85)	9	1.45 (0.68-3.10)	8	1.37 (0.61-3.07)
Duration of use										
<5 years	203	1.00 (0.84-1.20)	89	0.93 (0.71-1.21)	41	0.88 (0.60-1.31)	29	2.31 (1.31-4.06)	19	1.00 (0.54-1.82)
5-9 years	406	1.02 (0.89-1.17)	185	0.92 (0.75-1.13)	82	1.21 (0.89-1.65)	30	1.08 (0.64-1.82)	38	1.80 (1.08-3.03)
10+ years	103	1.02 (0.81-1.27)	40	0.78 (0.55-1.10)	20	1.10 (0.66-1.84)	11	1.61 (0.78-3.35)	8	2.46 (1.07-5.64)
Excluding the first 3 years of follow-up										
Never	335		153		63		24		11	
Ever	466	0.99 (0.85-1.14)	203	0.89 (0.71-1.11)	86	1.01 (0.72-1.42)	45	1.27 (0.75-2.14)	31	1.96 (0.96-4.02)
Duration of use										
<5 years	47	1.28 (0.92-1.77)	16	1.00 (0.58-1.71)	11	1.44 (0.70-2.93)	7	2.28 (0.93-5.62)	4	1.80 (0.55-5.90)
5-9 years	305	0.97 (0.82-1.14)	141	0.92 (0.72-1.17)	55	1.01 (0.69-1.47)	26	1.11 (0.62-1.99)	20	1.89 (0.87-4.08)
10+ years	91	0.96 (0.75-1.23)	35	0.75 (0.51-1.10)	18	1.01 (0.58-1.76)	9	1.36 (0.61-3.05)	6	3.11 (1.08-8.95)
Excluding women reporting mobile phone use in 1999-2000, as many may have subsequently changed use (see text and Figure 1)										
Never	295		151		49		18		17	
Ever	574	0.98 (0.84-1.13)	261	0.83 (0.68-1.02)	103	1.07 (0.75-1.52)	60	1.67 (0.97-2.86)	53	1.40 (0.80-2.44)
Duration of use										
<5 years	147	0.91 (0.74-1.13)	66	0.77 (0.57-1.06)	25	0.82 (0.49-1.38)	21	2.38 (1.19-4.74)	15	0.95 (0.46-1.94)
5-9 years	324	1.01 (0.85-1.18)	148	0.86 (0.68-1.09)	64	1.32 (0.89-1.94)	25	1.21 (0.65-2.27)	31	1.78 (0.96-3.29)
10+ years	67	0.96 (0.72-1.26)	29	0.75 (0.49-1.13)	9	0.85 (0.41-1.78)	7	1.77 (0.70-4.44)	5	1.98 (0.70-5.59)

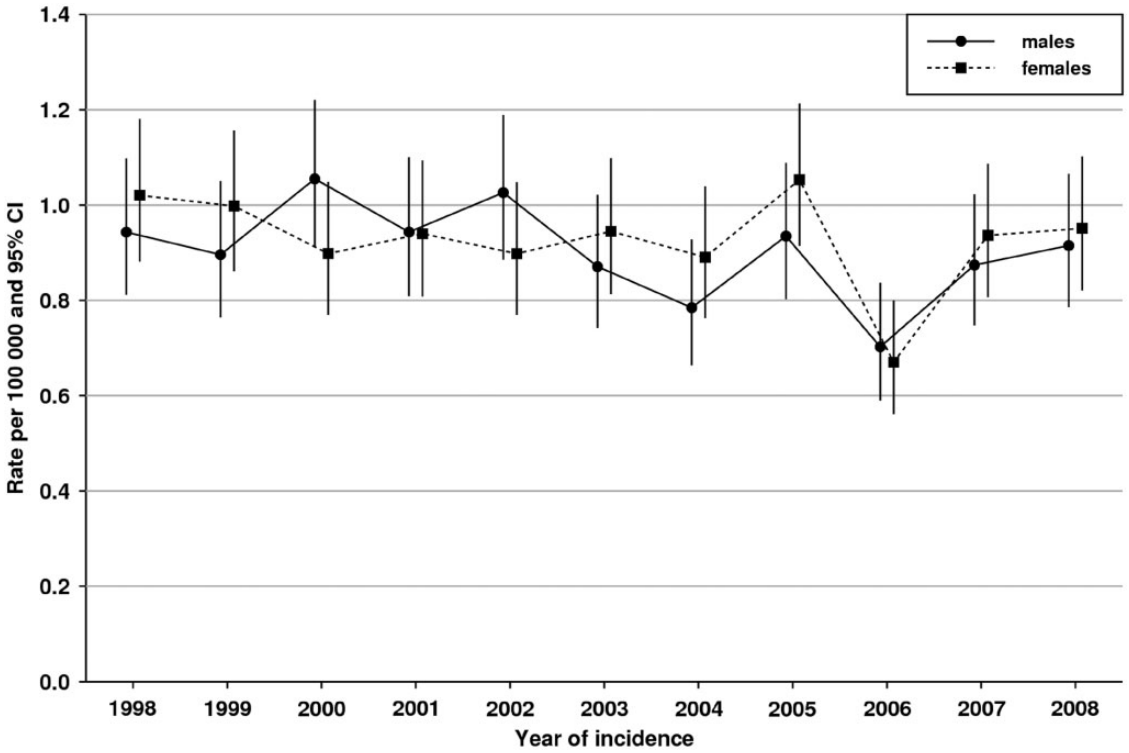

Figure 2 Annual incidence rates for acoustic neuroma (ICD-10 D33.3), for men and women aged 20–79 years, England, 1998 to 2008[12]

have cautioned against regarding this finding as strong evidence for a causal relationship. Also there has been no observable increase in glioma incidence during the past decade or so.[34,35]

For meningioma, our results and those from the Danish prospective study show no increase in the risk related to mobile phone use, with a combined RR of 0.97 (95% CI, 0.72–1.32, $P=0.86$) for 10 or more years of use. Studies with retrospective reporting of exposure have also found little evidence for increased risk of meningioma in mobile phone users.[27,30]

In contrast to the findings from the Danish prospective study,[11] we did find a trend of increasing risk for acoustic neuroma with increasing duration of mobile phone use. Acoustic neuroma is rare; there were relatively few incident acoustic neuromas in mobile phone users in either study (96 in our study and 261 in the Danish study), and confidence intervals surrounding each risk estimate are large. Combining results from the two studies gives a summary RR of 1.16 (95% CI 0.75–1.81, $P=0.50$) for mobile phone use for at least 10 years. With retrospective reporting of exposure, the INTERPHONE study found little evidence for increased risk of acoustic neuroma in mobile phone users. As in the analyses for glioma, their elevated odds ratio was found for acoustic neuroma only in those in the top decile of reported call time; and, again, no dose-response relationship was seen.[28] The Hardell group reported a relative risk of 2.9 (95% CI 1.6–5.5) for acoustic neuroma associated with the use of mobile phones for more than 10 years.[30] Acoustic neuroma often causes hearing loss: in the INTERPHONE study, 79% of acoustic neuroma patients reported having hearing problems before diagnosis, with 25% having had these symptoms for more than 5 years before diagnosis.[28] Given the media coverage of possible relationships between mobile phone use and brain tumours, it is possible that some of the observed associations are due to differential diagnosis, as long-term mobile phone users may have been selectively investigated for symptoms of hearing loss.

The rapidly increasing prevalence of mobile phone use in our cohort, from 34% in women reporting in 1999 to 79% in those reporting in 2005, is consistent with the steep increase in numbers of mobile phone subscriptions in the UK from the early 1990s to 2003[13] and mirrors similar increases in the rest of the world.[36] There is, however, little to suggest an increase in the incidence of acoustic neuroma in England between 1998 and 2008 (Figure 2).

We found a raised relative risk for pituitary tumours in ever users of mobile phones vs never users

(RR = 1.52, 95% CI 0.99–2.33, $P = 0.06$), but no evidence for a trend with increasing duration of use. Previous studies of incident pituitary tumours and mobile phone use have found no increase in risk.[37,38]

We found no evidence for increased incidence of other cancers in relation to use of a mobile phone, including cancers of the head and neck, all cancers, or cancer at 15 other specific sites, including malignant melanoma, leukaemia, multiple myeloma and non-Hodgkin lymphoma. These results are consistent with the limited published data for non-CNS tumours.[4,15–18,39] As found in the Danish cohort, mobile phone users in our study had a slightly lower incidence of lung cancer and all cancer than non-users; in the Million Women Study, mobile phone users were less likely than non-users to be current smokers at baseline, and it is possible that the slightly reduced risk of lung cancer reflects some residual confounding with smoking.

Mobile phone use was also not consistently associated with increased incidence of stroke or of ischaemic heart disease. The analyses of vascular disease risk were included largely for comparison with those for cancer. Although a case report of an indirect (mechanical) association between using a mobile phone and risk of cerebral ischaemia has been published,[40] we are not aware of any substantial hypothetical or reported direct associations between mobile phone use and vascular disease.

The main strengths of this study lie in the prospective collection of information on use of mobile phones, and the inclusion of large numbers who had used mobile phones for more than 5 years, and many for more than 10 years. As a prospective study with individual participant information on amount of mobile phone use and on possible confounders, this study was prone neither to the shortcomings of retrospective reporting of exposure nor to the limitations of the Danish prospective study, which was based on follow-up of subscription holders and had limited adjustment for other risk factors.[10] In previous analyses we have shown associations between height, body mass index and use of hormone therapy for menopause and risk of CNS tumours.[7,41,42] Obesity, physical activity, smoking and alcohol consumption are associated with risk of cancers at other sites. Some of these factors are related to reported mobile phone use and so could potentially confound associations between phone use and cancer risk, but we adjusted for these. Thus, with virtually complete follow-up, we were able to compare risks for a wide range of cancer outcomes in users and non-users of mobile phones, in an analysis free from recall bias and adjusted for potential confounding factors.

The main limitation of the study is that mobile phone use was reported at baseline and may have changed subsequently. Almost all women who reported daily use of mobile phones at baseline were still using a mobile phone at least once a week when asked again 8.8 years later. However, some women who reported not using a mobile phone at baseline began use subsequently; and this might dilute our estimates of relative risk towards the null. Our data suggest that, as expected, this problem is likely to be greatest among women who reported their baseline use of mobile phones in 1999 and 2000, before use became widespread; however, excluding these women did not materially alter our results. We did not have details of handedness of phone use, nor information on tumour laterality. Despite the large study size, the numbers of incident intracranial CNS tumours were still relatively small, especially for rarer tumours such as acoustic neuroma.

In conclusion, in this large prospective study we found no increase in the risk of glioma or meningioma, consistent with findings from the only other prospective study. We did find an increase in the risk of acoustic neuroma among those who had used mobile phones for 5 years or longer; but risk for acoustic neuroma in long-term mobile phone users was not significantly increased when our results were combined with those from the only other published prospective study. In relation to previous studies,[1] our results weaken the evidence for an association between mobile phone use and risk of glioma, but leaves open the possibility of an increased risk of acoustic neuroma in long-term users of mobile phones.

Supplementary Data

Supplementary data are available at *IJE* online.

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Conflict of interest: None declared.

KEY MESSAGES

- Results from some retrospective studies suggest a possible increased risk of glioma and acoustic neuroma in users of mobile phones. Interpretation of these findings is debated.
- In this large UK cohort study with prospective recording of mobile phone use, we found no association of phone use, including use for 10 or more years, with risk of incident glioma or meningioma, or of invasive cancer overall and at 18 specified sites.
- Risk of acoustic neuroma was increased in women with 5 or more years' mobile phone use, the risk increasing with increasing duration of use.
- Interpretation of the increased risk of acoustic neuroma is not straightforward. Acoustic neuroma registration rates in the UK have not changed over the period of rapidly increasing use of mobile telephones.

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