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Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study

The INTERPHONE Study Group*

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Background The rapid increase in mobile telephone use has generated concern about possible health risks related to radiofrequency electromagnetic fields from this technology.

Methods An interview-based case–control study with 2708 glioma and 2409 meningioma cases and matched controls was conducted in 13 countries using a common protocol.

Results A reduced odds ratio (OR) related to ever having been a regular mobile phone user was seen for glioma [OR 0.81; 95% confidence interval (CI) 0.70–0.94] and meningioma (OR 0.79; 95% CI 0.68–0.91), possibly reflecting participation bias or other methodological limitations. No elevated OR was observed $\geqslant$10 years after first phone use (glioma: OR 0.98; 95% CI 0.76–1.26; meningioma: OR 0.83; 95% CI 0.61–1.14). ORs were $<$1.0 for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the 10th decile of recalled cumulative call time, $\geqslant$1640 h, the OR was 1.40 (95% CI 1.03–1.89) for glioma, and 1.15 (95% CI 0.81–1.62) for meningioma; but there are implausible values of reported use in this group. ORs for glioma tended to be greater in the temporal lobe than in other lobes of the brain, but the CIs around the lobe-specific estimates were wide. ORs for glioma tended to be greater in subjects who reported usual phone use on the same side of the head as their tumour than on the opposite side.

Conclusions Overall, no increase in risk of glioma or meningioma was observed with use of mobile phones. There were suggestions of an increased risk of glioma at the highest exposure levels, but biases and error prevent a causal interpretation. The possible effects of long-term heavy use of mobile phones require further investigation.

Keywords Brain tumours, mobile phones, radiofrequency fields

Introduction

Mobile phone use has increased dramatically in many countries since its introduction in the early-to-mid 1980s. The expanding use of this technology has been accompanied by concerns about health and safety. In the late 1990s, several expert groups critically reviewed the evidence on health effects of low-level exposure to radiofrequency (RF)

electromagnetic fields, and recommended research into the possible adverse health effects of mobile telephony.[1–4] As a result, the International Agency for Research on Cancer (IARC) coordinated a feasibility study in 1998 and 1999, which concluded that an international study of the relationship between mobile phone use and brain tumour risk would be feasible and informative.[5,6]

INTERPHONE was therefore initiated as an international set of case–control studies focussing on four types of tumours in tissues that most absorb RF energy emitted by mobile phones: tumours of the brain (glioma and meningioma), acoustic nerve (schwannoma) and parotid gland. The objective was to determine whether mobile phone use increases the risk of these tumours and, specifically, whether RF energy emitted by mobile phones is tumourigenic.

This article presents the results of analyses of brain tumour risk in relation to mobile phone use in all INTERPHONE study centres combined. Analyses of brain tumours in relation to mobile phone use have been reported from a number of cohort[7–9] and case–control studies, including several of the national components of INTERPHONE.[10–25] No studies, however, have included as many exposed cases, particularly long-term and heavy users of mobile phones, as this study.

Methods

Study design

The INTERPHONE study is an international, largely population-based case–control study. The common core study protocol is described in detail elsewhere.[5,26] Sixteen study centres from 13 countries (Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK) were included. To maximize statistical power, the INTERPHONE study focussed on tumours in younger people, 30–59 years of age, as they were expected to have had the highest prevalence of mobile phone use in the previous 5–10 years, and on regions likely to have the longest and highest use of mobile phones (mainly large urban areas).

Eligible cases were all patients with a glioma or meningioma of the brain diagnosed in the study regions during study periods of 2–4 years between 2000 and 2004. Cases were ascertained from all neurological and neurosurgical facilities in the study regions (except in Paris and Tokyo where some did not agree to participate), and in some centres also from cancer registries. All diagnoses were histologically confirmed or based on unequivocal diagnostic imaging. To facilitate interviews soon after diagnosis, cases were ascertained actively within treatment facilities wherever possible. Completeness of ascertainment was checked through secondary sources, such as population- or hospital-based cancer registries, medical archives and hospital discharge or billing files.[26]

One control was selected for each case from a locally appropriate population-based sampling frame, except in Germany where two controls were chosen. The sampling procedure involved individual matching in seven centres (Canada – Ottawa, Canada – Vancouver, France, Israel, Japan, New Zealand and UK North) and frequency matching elsewhere. The matching variables were age (within 5 years), sex and region of residence within each study centre. In Israel, the subjects were also matched on ethnic origin. Where stratified matching had been used, individual matching was conducted *post hoc*, with cases being assigned one control (two in Germany), interviewed as close as possible in time to the case, from those who fitted the matching criteria.

Detailed information on past mobile phone use was collected during face-to-face interviews with the study subject, or a proxy, if the subject had ever been a regular user of a mobile phone (had an average of at least one call per week for a period of $\geqslant$6 months).[26] A proxy was sought when the study subject had died or was too ill to be interviewed. The interviews were conducted by a trained interviewer using a computer-assisted questionnaire, except in Finland where a paper version was used. The questionnaire also included sections on socio-demographic factors, occupational exposure to electromagnetic fields and ionizing radiation, medical history (subject's and family), medical ionizing and non-ionizing radiation exposure and smoking. For cases, information was also collected on the anatomic location and histological type of the tumours. Where possible, location data were obtained from magnetic resonance imaging (MRI) reports or images; they were otherwise obtained from surgical records or clinical notes. Details of the specific source for each case were not recorded in the INTERPHONE database. Those collecting the data did not know the reported mobile phone use of individual cases.

Statistical methods

Data from countries with multiple centres were combined for the analyses, except in the UK where the UK South and UK North, each with large numbers of subjects, were kept separate. The word 'centre' in the remainder of this article is used to refer to the 14 analytic entities (12 countries, UK North and UK South). All analyses were carried out for all centres combined and for each centre separately. Formal tests for heterogeneity of risk across centres were conducted by allowing for an interaction between centre and the exposure variables.

The analyses presented here focus on past mobile phone use as reported by or for the study subjects. The main analyses were based on conditional logistic regression for matched sets.[27] The date of diagnosis of the case was used as the reference date for cases and

controls in each matched set. For the main analyses, the reference category for odds ratios (ORs) was the set of subjects who reported that they had never been regular users. Exposure variables included ever having been a regular user (as defined above), time (years) since first regular use, cumulative number of calls and cumulative duration of calls. To allow for a latency period of 1 year, the year before the reference date was included in the reference category for time since first regular use and all other exposure variables were censored at 1 year before the reference date. Cumulative number and duration of calls were analysed as categorical variables, based on deciles of the distribution of these variables among all controls who were regular users, including those matched to patients with an acoustic neuroma or a parotid gland tumour, so that the same cut-off points are used in all analyses.[26] Cumulative use excluded use of mobile phones with hands-free devices: for all time periods for which the subject reported the use of hands-free devices the amount of use was reduced by 100, 75, 50 or 25% depending on whether hands-free devices were used always or almost always, more than half, about half or less than half of the time, respectively. For ease of presentation, some results are shown for the following grouping of deciles: 1, 2–5, 6–7, 8–9 and 10, chosen *post hoc* to reflect the spread of the highly skewed distribution of these variables. For convenience, we will systematically use the term 'regular user' in text and tables to refer to ever having been a regular user.

The reference group for these analyses, never regular users, included people who had some mobile phone use but never as much as one call a week on average for $\geqslant$6 months (~32% of meningioma and 26% of glioma cases, and 30% of meningioma and 26% of glioma controls) and people who had never used a mobile phone (~11% of meningioma and 9% of glioma cases, and 8% of meningioma and 6% of glioma controls). These percentages are approximate because never use and never regular use were defined at different dates; the reference date and the date of interview, respectively. We are not able to determine whether inclusion of subjects with some occasional mobile phone use in the reference group had a material effect on our results because this difference in definition dates prevented us from distinguishing participants with only occasional use from those with no use at all at their reference dates. Moreover, because numbers of never users at the date of interview were small, particularly in certain age- and gender-specific sub-groups (such as young men), never users were not a suitable reference group for this analysis.

All analyses were adjusted for educational level; an a priori decision had been made to adjust for it as a surrogate for socio-economic status (SES). Creation of consistent educational levels across the 13 countries is described elsewhere.[26] In practice, this adjustment had little impact on OR estimates, changing their values by $\leqslant$2% in most instances and in all cases by <5%. Using a 10% change-in-estimate criterion for confounding,[28] no other covariate among those collected (see list above) was included in the main analyses. The interval between the start date of interviews in the study centre and the date of each subject's interview was modelled by fitting the interaction of this interval with study centre.

A common protocol was applied to impute missing data for cases and controls.[26] The study questionnaire allowed ranges to be given instead of exact answers to a number of questions, including number and duration of calls and dates of start and end of mobile phone use; in such instances, the main analyses in this article were based on the mid-point of the reported range.

Because absorption of RF energy from mobile phones is highly localized,[29] three different types of analyses were conducted to account for tumour location. First, analyses were conducted by the anatomical lobe of the brain in which the tumour occurred. Secondly, separate analyses were conducted for the subjects who reported using the mobile phone mainly on one or the other side of the head, and the preferred side was compared with the side on which the tumour occurred. For this, each control was assigned the location of the tumour of his or her matched case. Exposure was considered to be ipsilateral if the phone was used predominantly on the same side as the tumour or on both sides of the head, and contralateral if used mainly on the side of the head opposite to the tumour. Laterality was not assigned if the tumour was reported to be centrally located (i.e. it crossed the midline of the brain); these cases were excluded from laterality analyses. Thirdly, case–case analyses were carried out on the concordance between tumour side and laterality of phone use using the method proposed by Inskip and collaborators.[18]

Sensitivity analyses

To complement these primary analyses, we undertook sensitivity analyses to try to determine whether any of the following might have biased the results: (i) any study centre; (ii) required mention of mobile phones in the introductory letter to subjects in some centres; (iii) centres with a hospital-based design or particularly low participation rates; (iv) respondents whose interviews were considered by the interviewer to be of poor quality; (v) subjects for whom proxies provided the responses or a telephone interview was given; (vi) interviewers who had little experience or who had unbalanced case to control workloads; (vii) difference between the interview dates of cases and their matched controls (on average, each control was interviewed 3 months later than its matched case[26] and mobile phone use was increasing rapidly during the study period); (viii) subject's choice between two ways of responding to call time questions (time per

day, week or month, or time per call); (ix) subjects who reported implausibly high amounts of mobile phone use (by excluding them or by retaining them and truncating their use at a specific lower value when they reported a higher one); (x) method of calculating accumulated call time; (xi) use of matching and conditional analysis; (xii) the choice of a particular imputation algorithm; and (xiii) adjustment for possible confounders.

Results

During the study period, 3115 meningioma and 4301 glioma cases, and 14 354 potential controls were identified. Interviews were completed with 2425 meningioma cases (78%; range 56–92%), 2765 glioma cases (64% participation; range by centre 36–92%) and 7658 controls (53%; range 42–74%; Appendix 1, Table 1, Supplementary data are available at *IJE* online). The most common reasons for non-participation were subject refusal (11% of meningiomas, 11% of glioma cases and 30% of controls); illness, death or physician refusal (4% of meningiomas, 20% of gliomas and 1% of controls); and inability to contact the subject (7% of meningiomas, 5% of gliomas and 15% of controls).

The main analyses, based on matched sets only, included 2409 meningioma cases with 2662 matched controls and 2708 glioma cases with 2972 matched controls. Among meningioma cases, 24% were men and 76% women; among glioma cases, 60% were men and 40% women (Table 1). Although the median age of meningioma cases was only slightly older than that of glioma cases (51 and 49 years, respectively), 23% of glioma cases were diagnosed before the age of 40, compared with 13% of meningioma cases.

The proportion of proxy interviews was higher in glioma cases (13%) than in controls (1%) or meningioma cases (2%). Whereas 17% of glioma cases who were regular users had imputations because of missing information in at least one of their mobile phone-related variables, the corresponding fractions were 9% among regular user meningioma cases and 8% among regular user controls. The proportion of subjects who answered questions about mobile phone use by giving a range of values rather than a particular amount of use (for any of the use dimensions) was very similar (~42%) for meningioma cases, glioma cases and controls.

The prevalence of regular mobile phone use 1 year before the reference date was 52% for meningioma cases (ranging from 34 to 73% across study centres) and 56% in matched controls (35–78%). It was higher for glioma cases (62% overall, range: 42–80%) and controls (64% overall, range: 45–84%), reflecting the different sex distributions of these tumours.

The majority of subjects in the study were not heavy mobile phone users; the median lifetime cumulative call time among meningioma controls using mobile phones was ~75 h, with a median call time of ~2 h/month and a median lifetime number of calls about 1500. Corresponding values for glioma controls were ~100 h lifetime, 2.5 h/month and about 2000 calls. The distributions of time since start of mobile phone use and cumulative call time were highly skewed, with few long-term and heavy users, and varied across study centres and by age and sex (not shown).

Relation between mobile phone use and risk of brain tumours

Meningioma

A reduced OR of meningioma was found for regular mobile phone use in the past $\geqslant$1 year, OR 0.79 [95% confidence interval (CI) 0.68–0.91; Table 2]. There was some suggestion of heterogeneity of risk across centres ($P = 0.08$) with ORs <1.0 except in Canada, Denmark, Germany and Italy (data not shown). ORs were <1.0 for regular users in all categories of time since start of use and cumulative number of calls. Analyses by cumulative call time showed ORs <1.0 in the first nine deciles and an OR of 1.15 (95% CI 0.81–1.62) in the highest decile. Analyses of cumulative call time among recent-, medium- and long-term users (Table 3) showed no indication of excess risk except in the highest call time category in those who started phone use 1–4 years before the reference date: OR 4.80 (95% CI 1.49–15.4).

There was no appreciable effect modification by age or sex on any of these results (data not shown).

In analyses by anatomical location of the meningioma, the OR for temporal lobe tumours with regular use was 0.55 (95% CI 0.36–0.82) and the ORs were <1.0 in all categories of time since start of use, cumulative call time and cumulative number of calls. ORs for other lobes were also mostly <1.0 (Table 4).

The OR for mainly ipsilateral use among regular users was 0.86 (95% CI 0.69–1.08), and that for contralateral use was 0.59 (95% CI 0.46–0.76; Table 5). The ORs by time since start of use were <1.0 in all categories of ipsilateral and contralateral use. When analysing by any of the exposure metrics in Table 5, the ratios of the ORs for ipsilateral use to contralateral use were always one or above one regardless of level of exposure and they were highest (~2 or 3) for the two highest categories of cumulative call time and the second highest category of cumulative number of calls. A case–case analysis, based on Inskip's method, showed an OR of 1.07 (95% CI 1.00–1.16; Appendix 1, Table 2, Supplementary data are available at *IJE* online) for ipsilateral use.

The OR for those who reported regular use of only an analogue phone was 0.81 (95% CI 0.65–1.03) and for only a digital phone it was 0.79 (95% CI 0.68–0.92). Focussing on the highest decile of cumulative call time, the OR among those who used only an analogue phone was 0.50 (95% CI 0.25–0.99); among

Table 1 Selected characteristics of meningioma and glioma cases included in the main analyses[a]

Characteristics of the study population	Meningioma *n* (%)	Glioma *n* (%)
All interviewed cases	2425 (100)	2765 (100)
Cases included in main analysis[b]	2409 (99)	2708 (98)
Cases with histological confirmation	2249 (93)	2659 (98)
Demographic characteristics		
Men	572 (24)	1624 (60)
Women	1837 (76)	1084 (40)
Aged 30–39 years at diagnosis	316 (13)	635 (23)
Aged 40–49 years at diagnosis	806 (33)	841 (31)
Aged 50–59 years at diagnosis	1287 (53)	1232 (45)
Distribution by country		
Australia	253 (11)	296 (11)
Canada	94 (4)	170 (6)
Denmark	124 (5)	179 (7)
Finland	231 (10)	177 (7)
France	144 (6)	94 (3)
Germany	250 (10)	256 (9)
Israel	350 (15)	180 (7)
Italy	110 (5)	118 (4)
Japan	82 (3)	60 (2)
New Zealand	52 (2)	83 (3)
Norway	143 (6)	154 (6)
Sweden	183 (8)	222 (8)
UK North	173 (7)	421 (16)
UK South	220 (9)	298 (11)

[a]The controls for each case series have the same distributions of characteristics as the cases to which they are matched.
[b]Excluded are cases for whom no controls could be found (55 for glioma and 15 for meningioma) and cases in matched sets (two for glioma and one for meningioma), where the regular use status of the case or the control was unknown.

those who used only a digital phone it was 1.84 (95% CI 1.17–2.88); and among those using both 4.43 (95% CI 1.42–13.9; Appendix 1, Table 3, Supplementary data are available at *IJE* online).

Glioma

A reduced risk of glioma was seen for regular mobile phone use in the past $\geqslant 1$ year (OR 0.81, 95% CI 0.70–0.94; Table 2) relative to never regular users. There was little evidence of heterogeneity in results across centres ($P = 0.68$). ORs were <1.0 in all study centres except Australia, France and New Zealand.

Analyses by time since start of use showed a reduced OR in all categories of use; the OR for $\geqslant 10$ years since start of use was 0.98 (95% CI 0.76–1.26; Table 2). The pattern of results by duration of mobile phone use was similar (data not shown).

Analyses by categories of cumulative call time showed decreased ORs in eight of the first nine deciles (five of which had upper confidence bounds <1.0) and an increased OR of 1.40 (95% CI 1.03–1.89) in the highest exposure category, $\geqslant 1640$ h. Analyses by cumulative number of calls showed ORs <1.0 in all categories, with the OR in the highest decile approaching unity.

Analyses of cumulative call time stratified by short-, medium- and long-term use (Table 3) showed reduced risks in the lower call time categories in all strata of time since start of use and ORs >1.0 in the highest category ($\geqslant 1640$ h cumulative call time) in each of the three strata. The highest OR was in the short-term users but its CI was very wide.

The lobe of the brain in which the tumour was located was known for 96% of cases. The OR for temporal lobe tumours with regular use was 0.86 (95% CI 0.66–1.13; Table 4). The point estimates for the highest categories of cumulative call time, cumulative number of calls and time since start of use were higher for tumours in the temporal lobe than in other locations, but their 95% CIs were wide. Only

Table 2 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by regular use, time since start of use, cumulative call time and cumulative number of calls—excludes use with hands-free devices

	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Regular use in the past ⩾1 year						
No	1147	1174	1.00	1042	1078	1.00
Yes	1262	1488	0.79 (0.68–0.91)	1666	1894	0.81 (0.70–0.94)
Time since start of use (years)						
Never regular user	1147	1174	1.00	1042	1078	1.00
1–1.9	178	214	0.90 (0.68–1.18)	156	247	0.62 (0.46–0.81)
2–4	557	675	0.77 (0.65–0.92)	644	725	0.84 (0.70–1.00)
5–9	417	487	0.76 (0.63–0.93)	614	690	0.81 (0.60–0.97)
⩾10	110	112	0.83 (0.61–1.14)	252	232	0.98 (0.76–1.26)
Cumulative call time with no hands-free devices (h)[b]						
Never regular user	1147	1174	1.00	1042	1078	1.00
<5 h	160	197	0.90 (0.69–1.18)	141	197	0.70 (0.52–0.94)
5–12.9	142	159	0.82 (0.61–1.10)	145	198	0.71 (0.53–0.94)
13–30.9	144	194	0.69 (0.52–0.91)	189	179	1.05 (0.79–1.38)
31–60.9	122	145	0.69 (0.51–0.94)	144	196	0.74 (0.55–0.98)
61–114.9	129	162	0.75 (0.55–1.00)	171	193	0.81 (0.61–1.08)
115–199.9	96	155	0.69 (0.50–0.96)	160	194	0.73 (0.54–0.98)
200–359.9	108	133	0.71 (0.51–0.98)	158	194	0.76 (0.57–1.01)
360–734.9	123	133	0.90 (0.66–1.23)	189	205	0.82 (0.62–1.08)
735–1639.9	108	103	0.76 (0.54–1.08)	159	184	0.71 (0.53–0.96)
⩾1640	130	107	1.15 (0.81–1.62)	210	154	1.40 (1.03–1.89)
Cumulative number of calls with no hands-free devices (in hundreds)[b]						
Never regular user	1147	1174	1.00	1042	1078	1.00
$<1.5 \times 100$ calls	159	180	0.95 (0.72–1.27)	147	182	0.74 (0.55–0.99)
1.5–3.4	136	182	0.62 (0.46–0.83)	141	200	0.71 (0.54–0.95)
3.5–7.4	148	176	0.90 (0.68–1.19)	161	201	0.76 (0.58–1.00)
7.5–13.9	143	173	0.80 (0.61–1.07)	174	179	0.90 (0.68–1.20)
14–25.4	122	181	0.60 (0.45–0.81)	180	206	0.78 (0.59–1.02)
25.5–41.4	111	126	0.81 (0.58–1.13)	156	190	0.83 (0.62–1.10)
41.5–67.9	129	146	0.79 (0.58–1.09)	163	194	0.71 (0.53–0.94)
68–127.9	134	126	0.92 (0.67–1.26)	186	200	0.93 (0.70–1.23)
128–269.9	100	100	0.81 (0.57–1.16)	193	180	0.96 (0.72–1.28)
⩾270	80	98	0.80 (0.55–1.17)	165	162	0.96 (0.71–1.31)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[b]Categories are based on the deciles of the distribution among all eligible regular user controls (see text).

for the highest decile of cumulative call time was the OR for temporal lobe tumours appreciably elevated (1.87, 95% CI 1.09–3.22).

For regular use in the past ⩾1 year, the OR for ipsilateral mobile phone use was 0.84 (95% CI 0.69–1.04) and that for contralateral use was 0.67 (95% CI 0.52–0.87; Table 5). The ORs by time since start of use were <1.0 in all categories, except for ipsilateral use beginning ⩾10 in the past (OR 1.21, 95% CI 0.82–1.80). The ORs by cumulative number of calls were <1.0 irrespective of laterality and exposure level, except for ipsilateral use in the two highest categories. The results by cumulative call time showed a similar pattern, but the OR for ipsilateral use in the highest category was appreciably elevated (OR 1.96, 95% CI 1.22–3.16) and that for contralateral use was slightly elevated (OR 1.25, 95% CI 0.64–2.42). The ratios of the ipsilateral ORs to the contralateral

Table 3 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by cumulative call time, stratified by recency of starting regular use—excludes use with hands-free devices

	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Cumulative Call time (h)						
	Non-regular users					
	1147	1174	1.00	1042	1078	1.00
	Short-term users: start of phone use 1–4 years before reference date					
<5 h	150	186	0.92 (0.69–1.22)	127	182	0.68 (0.50–0.93)
5–114.9	401	500	0.74 (0.61–0.90)	449	533	0.82 (0.67–0.99)
115–359.9	95	126	0.79 (0.55–1.12)	121	154	0.74 (0.52–1.03)
360–1639.9	67	72	0.77 (0.49–1.20)	80	95	0.75 (0.50–1.13)
⩾1640	22	5	4.80 (1.49–15.4)	23	8	3.77 (1.25–11.4)
	Medium-term users: start of phone use 5–9 years before reference date					
<5 h	7	9	0.67 (0.23–1.96)	10	13	0.86 (0.32–2.28)
5–114.9	122	145	0.73 (0.54–0.98)	180	208	0.86 (0.66–1.12)
115–359.9	95	140	0.67 (0.48–0.93)	156	192	0.71 (0.53–0.95)
360–1639.9	129	131	0.83 (0.60–1.14)	174	204	0.72 (0.54–0.95)
⩾1640	64	62	1.03 (0.65–1.65)	94	73	1.28 (0.84–1.95)
	Long-term users: start of phone use ⩾10 years before reference date					
<5 h	3	2	1.31 (0.21–8.07)	4	2	1.13 (0.16–7.79)
5–114.9	14	15	0.79 (0.36–1.73)	20	25	0.63 (0.32–1.25)
115–359.9	14	22	0.49 (0.24–1.01)	41	42	0.89 (0.53–1.50)
360–1639.9	35	33	1.00 (0.58–1.72)	94	90	0.91 (0.63–1.31)
⩾1640	44	40	0.95 (0.56–1.63)	93	73	1.34 (0.90–2.01)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.

ORs were all above one with one exception (0.99 for 2–4 years since start of use) and the highest (~2) were in 1–1.9 and ⩾10 years since start of use, the lowest category of cumulative call time, and the highest category of cumulative number of calls. For cumulative number of calls, there was a consistent trend towards increasing ratios with increasing exposure.

Case–case analyses of the concordance between tumour side and preferred side of phone use using the Inskip method showed an elevated risk for ipsilateral use among regular users (OR 1.27, 95% CI 1.19–1.37) and among those in the highest decile of cumulative call time (OR 1.55, 95% CI 1.24–1.99; Appendix 1, Table 2, Supplementary data are available at *IJE* online). When stratified on time since first use, the point estimate of the OR using Inskip's method in the highest decile was higher among short-term heavy users (OR 2.37, 95% CI 0.93–8.59) than among medium (OR 1.40, 95% CI 1.04–2.01) and long-term (OR 1.57, 95% CI 1.13–2.30) heavy users, resembling an analogous pattern in Table 3.

The OR for ever use of an analogue phone was 1.00 (95% CI 0.83–1.21) and for ever use of a digital phone 0.76 (95% CI 0.66–0.88). Increased ORs were seen in the highest decile of cumulative call time with analogue phones (OR 1.95, 95% CI 1.08–3.54) and with digital phones (OR 1.46, 95% CI 0.98–2.17; Appendix 1, Table 3, Supplementary data are available at *IJE* online).

There was no evidence of heterogeneity of effects across centres for cumulative call time, cumulative number of calls, time since start of use or ipsilateral or contralateral use. Nor was there any appreciable effect modification by age or sex in any of the results mentioned above (data not shown).

Sensitivity analyses

Selected findings of sensitivity analyses are shown in Table 6 and Appendix 1, Table 4 (Supplementary data are available at *IJE* online). Because of a hint of a possible excess risk in subjects in the highest decile of mobile phone cumulative call time, for glioma (OR 1.40) and to a lesser extent for meningioma (OR 1.15), we focus presentation of sensitivity analyses on the findings in this highest decile, corresponding to 1640 or more cumulative hours of use.

For meningioma, some point estimates differed from the OR of 1.15 from the main analysis, but the estimates were imprecise and, with one exception based

Table 4 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by anatomical location of tumour[a] and by regular use, time since start of use, cumulative call time and cumulative number of calls – excludes use with hands-free devices

	Meningioma									Glioma								
	Tumour in temporal lobe			Tumour in parietal or frontal lobes			Tumour in other locations			Tumour in temporal lobe			Tumour in parietal or frontal lobes			Tumour in other locations		
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)
Regular use in the past ⩾1 year																		
No	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
Yes	190	262	0.55 (0.36–0.82)	590	701	0.79 (0.63–0.99)	300	348	0.76 (0.56–1.04)	509	568	0.86 (0.66–1.13)	871	998	0.77 (0.62–0.95)	212	248	0.79 (0.51–1.23)
Time since start of use (years)																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
1–1.9	27	40	0.60 (0.29–1.27)	82	103	0.70 (0.46–1.06)	44	50	1.12 (0.63–1.99)	51	69	0.87 (0.54–1.41)	74	138	0.45 (0.30–0.70)	23	32	0.67 (0.30–1.47)
2–4	95	145	0.55 (0.34–0.89)	256	283	0.85 (0.65–1.12)	137	163	0.72 (0.50–1.06)	175	211	0.77 (0.55–1.08)	347	386	0.83 (0.64–1.08)	95	95	0.94 (0.57–1.52)
5–9	56	65	0.49 (0.27–0.88)	199	252	0.74 (0.56–1.00)	94	116	0.62 (0.40–0.94)	189	219	0.80 (0.56–1.13)	321	358	0.78 (0.60–1.02)	74	89	0.70 (0.40–1.22)
⩾10	12	12	0.60 (0.22–1.62)	53	63	0.76 (0.48–1.20)	25	19	1.02 (0.48–2.16)	94	69	1.36 (0.88–2.11)	129	116	0.92 (0.65–1.30)	20	32	0.41 (0.16–1.08)
Cumulative call time (h)[c]																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
<5 h	23	41	0.49 (0.24–1.01)	72	87	0.88 (0.58–1.33)	43	45	1.13 (0.64–1.99)	45	59	0.67 (0.40–1.13)	70	105	0.65 (0.42–1.01)	20	25	0.87 (0.37–2.04)
5–114.9	89	123	0.59 (0.36–0.97)	260	297	0.76 (0.58–0.98)	120	158	0.64 (0.44–0.93)	191	234	0.88 (0.63–1.21)	326	406	0.72 (0.56–0.93)	99	96	0.85 (0.52–1.38)
115–359.9	24	52	0.28 (0.13–0.59)	90	140	0.71 (0.49–1.03)	48	60	0.75 (0.43–1.31)	95	104	0.84 (0.55–1.28)	178	213	0.70 (0.51–0.96)	34	51	0.70 (0.35–1.40)
360–1639.9	33	32	0.75 (0.36–1.56)	111	118	0.82 (0.57–1.18)	56	59	0.71 (0.42–1.21)	100	124	0.71 (0.47–1.07)	192	189	0.87 (0.64–1.19)	41	58	0.63 (0.30–1.30)
⩾1640	21	14	0.94 (0.31–2.86)	57	59	1.08 (0.65–1.80)	33	26	1.05 (0.52–2.14)	78	47	1.87 (1.09–3.22)	105	85	1.25 (0.81–1.91)	18	18	0.91 (0.33–2.51)
Cumulative number of calls (in hundreds)[c]																		
Never regular user	207	218	1.00	520	513	1.00	282	297	1.00	311	339	1.00	551	551	1.00	141	155	1.00
<1.5 × 100 calls	26	35	0.66 (0.32–1.37)	73	87	0.83 (0.54–1.26)	41	39	1.30 (0.72–2.34)	44	54	0.72 (0.42–1.23)	74	95	0.65 (0.42–1.02)	19	25	0.82 (0.34–1.95)
1.5–25.4	85	128	0.57 (0.35–0.94)	262	311	0.77 (0.59–0.99)	127	175	0.64 (0.44–0.92)	191	235	0.83 (0.60–1.15)	334	423	0.69 (0.54–0.89)	106	98	0.91 (0.57–1.47)
25.5–67.9	24	58	0.28 (0.13–0.58)	114	121	0.94 (0.65–1.35)	57	57	0.73 (0.44–1.23)	96	113	0.81 (0.55–1.21)	176	207	0.76 (0.55–1.03)	34	44	0.63 (0.31–1.26)
68–269.9	43	25	0.88 (0.42–1.85)	106	129	0.71 (0.49–1.03)	56	55	0.80 (0.47–1.37)	117	110	1.04 (0.69–1.55)	201	191	0.95 (0.70–1.30)	41	62	0.63 (0.30–1.32)
⩾270	12	16	0.51 (0.19–1.38)	35	53	0.74 (0.42–1.31)	19	22	0.87 (0.37–2.04)	61	56	1.10 (0.65–1.85)	86	82	1.02 (0.67–1.57)	12	19	0.42 (0.13–1.33)

[a]A total of 115 gliomas and 357 meningiomas with unknown anatomical location are not included.
[b]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[c]Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2–5, 6–7, 8–9 and 10.

Table 5 ORs between mobile phone use and brain tumours (meningioma and glioma separately) by side of use of mobile phones and by regular use, time since start of use, cumulative call time and cumulative number of calls[a]

	Meningioma							Glioma						
	Ipsilateral phone use			Contralateral phone use			Ratio[c]	Ipsilateral phone use			Contralateral phone use			Ratio[c]
	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	ipsi/contra	Cases	Controls	OR[b] (95% CI)	Cases	Controls	OR[b] (95% CI)	ipsi/contra
Regular use in the past ⩾1 year														
No	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
Yes	424	479	0.86 (0.69–1.08)	281	406	0.59 (0.46–0.76)	1.46	677	753	0.84 (0.69–1.04)	328	437	0.67 (0.52–0.87)	1.25
Time since start of use (years)														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
1–1.9	54	79	0.71 (0.44–1.15)	41	59	0.67 (0.38–1.20)	1.06	69	91	0.77 (0.49–1.20)	24	58	0.38 (0.20–0.71)	2.03
2–4	198	203	0.89 (0.67–1.19)	118	196	0.54 (0.39–0.76)	1.65	261	300	0.80 (0.62–1.04)	145	178	0.81 (0.57–1.14)	0.99
5–9	132	155	0.87 (0.63–1.21)	100	126	0.64 (0.44–0.94)	1.36	239	280	0.81 (0.62–1.05)	110	145	0.65 (0.44–0.95)	1.25
⩾10	40	42	0.88 (0.52–1.47)	20	25	0.58 (0.29–1.16)	1.52	108	82	1.21 (0.82–1.80)	49	56	0.70 (0.42–1.15)	1.73
Cumulative call time with no hands-free devices (h)[d]														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
<5 h	48	71	0.76 (0.48–1.210	36	54	0.75 (0.42–1.31)	1.01	64	76	0.83 (0.53–1.31)	23	50	0.43 (0.22–0.84)	1.93
5–114.9	185	209	0.86 (0.65–1.15)	125	190	0.55 (0.40–0.75)	1.56	253	321	0.75 (0.58–0.97)	135	170	0.74 (0.53–1.03)	1.01
115–359.9	65	96	0.64 (0.42–0.97)	42	69	0.64 (0.39–1.06)	1.00	121	147	0.75 (0.53–1.07)	67	93	0.62 (0.39–0.97)	1.21
360–1639.9	80	68	1.09 (0.72–1.64)	50	65	0.55 (0.32–0.94)	1.98	139	147	0.88 (0.62–1.24)	64	93	0.60 (0.38–0.94)	1.47
⩾1640	46	35	1.45 (0.80–2.61)	28	28	0.62 (0.31–1.25)	2.34	100	62	1.96 (1.22–3.16)	39	31	1.25 (0.64–2.42)	1.57
Cumulative number of calls with no hands-free devices (in hundreds)[d]														
Not regular user	821	898	1.00	832	841	1.00		773	838	1.00	721	718	1.00	
<1.5 × 100 calls	51	72	0.77 (0.49–1.22)	32	49	0.76 (0.41–1.40)	1.01	61	71	0.66 (0.41–1.07)	26	44	0.61 (0.32–1.17)	1.08
1.5–25.4	187	229	0.80 (0.60–1.05)	131	191	0.59 (0.44–0.81)	1.36	263	318	0.80 (0.62–1.04)	138	179	0.69 (0.49–0.96)	1.16
25.5–67.9	80	81	0.89 (0.59–1.35)	51	77	0.61 (0.37–1.00)	1.46	115	159	0.69 (0.49–0.97)	64	91	0.59 (0.38–0.92)	1.17
68–269.9	76	61	1.22 (0.77–1.95)	49	66	0.39 (0.23–0.68)	3.13	164	145	1.09 (0.78–1.52)	72	86	0.81 (0.51–1.28)	1.35
⩾270	30	36	1.01 (0.56–1.82)	18	23	0.66 (0.30–1.46)	1.53	74	60	1.51 (0.91–2.51)	28	37	0.61 (0.32–1.18)	2.48

[a]Seventy-two glioma-matched sets and 43 meningioma-matched sets including subjects with unknown laterality of use or with cases with unknown side of tumour are excluded from these analyses. The reference category consists of subjects who were not regular users 1 year before the reference date. Because the main analyses in this article use matched conditional logistic regression, all matched sets in which the case and/or the control was a regular contralateral user are excluded from the ipsilateral analyses; similarly, sets in which the case and/or the control was a regular ipsilateral user are excluded from the contralateral analyses. This explains the differences in the numbers of cases and controls in the reference category and the fact that the number of ipsilateral and contralateral regular user cases (and controls) does not add up to the total number of regular users in the previous table.
[b]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[c]Ratio of OR for ipsilateral tumours to OR for contralateral tumours.
[d]Deciles of exposure used in Table 2 have been collapsed into six categories for these analyses: deciles 1, 2-5, 6-7, 8-9 and 10.

Table 6 Results of sensitivity analyses on ORs between mobile phone use and brain tumours (meningioma and glioma separately) for the highest decile of cumulative call time, covering possible indicators of sample representativeness and response quality

Factors included in sensitivity analyses	Meningioma			Glioma		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Main analysis (baseline for comparison)	130	107	1.15 (0.81–1.62)	210	154	1.40 (1.03–1.89)
Presentation of the study						
Explicit mention of mobile phones	62	61	0.91 (0.56–1.47)	101	81	1.30 (0.87–1.93)
Mobile phones mentioned, but not stressed	58	35	1.50 (0.86–2.59)	90	63	1.47 (0.89–2.44)
No mention of mobile phones	10	11	1.07 (0.17–6.83)	19	10	1.72 (0.38–7.85)
Participation rates						
Study centres with control participation rates <60%	75	45	1.44 (0.89–2.34)	142	99	1.39 (0.94–2.04)
Study centres with control participation rates ⩾60%	55	62	0.93 (0.56–1.55)	68	55	1.46 (0.89–2.39)
Excluding study centres with hospital based case ascertainment[b]	123	100	1.13 (0.80–1.60)	200	149	1.39 (1.02–1.88)
Quality and timing of interview						
Excluding proxy interviews	127	107	1.13 (0.80–1.59)	188	138	1.46 (1.05–2.04)
Excluding telephone interviews	120	103	1.04 (0.72–1.49)	194	150	1.30 (0.95–1.78)
With experienced interviewers only[c]	116	97	1.09 (0.76–1.56)	201	139	1.50 (1.10–2.06)
Balanced interviewer workload[d]	95	73	1.13 (0.75–1.69)	164	119	1.38 (0.97–1.96)
Control interviews within 1 month of case interview	35	21	1.32 (0.70–2.48)	46	30	1.43 (0.79–2.57)
Interviewer judgement of quality of response[e]						
Excluding non-responsive study subjects or subjects with poor memory	91	75	1.28 (0.85–1.93)	130	92	1.38 (0.94–2.03)
Duration of call time						
When answered by day/week/month	9	4	5.78 (0.81–41.06)	9	3	6.08 (0.72–51.65)
When answered by call	112	94	1.00 (0.69–1.45)	177	136	1.23 (0.89–1.70)
Truncation of phone use to 5 h/day[f]	130	107	1.15 (0.81–1.62)	208	153	1.38 (1.02–1.87)
Truncation of phone use to 1 h/day[f]	80	75	1.06 (0.70–1.60)	144	104	1.41 (0.99–1.99)
Assuming call time per day only concerns work days[g]	136	117	1.08 (0.78–1.51)	225	167	1.31 (0.98–1.75)
Exclusion of subjects who reported >5 h/per day[f]	106	94	1.02 (0.70–1.48)	169	134	1.27 (0.92–1.75)
Use of imputation and ranges						
Excluding responses with imputed items	104	81	1.21 (0.82–1.78)	157	115	1.34 (0.96–1.88)
Using minimum rather than median when range given	97	88	1.08 (0.74–1.58)	140	105	1.35 (0.94–1.93)

[a]ORs adjusted for sex, age, study centre, ethnicity in Israel and education.
[b]Japan and France–Paris excluded.
[c]Included only interviewers who conducted at least 20 interviews.
[d]Included only interviewers whose case/control interview ratio was between 1/4 and 3/4 (between 1/6 and 5/6 in Germany where two controls were matched to each case).
[e]Restricted to study subjects who the interviewers judged to be fairly or very cooperative and responsive and who were judged to remember fairly well, well or very well both their current and past mobile phone use history.
[f]Truncation and exclusion were based on all use of a mobile phone; that is, including when using hands-free devices.
[g]Working days were assumed to be 5.5 days/week for 50 weeks of the year and new deciles were created to reflect the changed total hours.

on nine cases and four controls, fell well within the CI of this 'benchmark' value.

For glioma, results from the various sensitivity analyses were generally similar to those from the primary analysis. All the OR estimates, except one based on nine cases and three controls, are well within the 95% CI of the OR from the main analysis. When subjects with high reported use were included, but with use truncated at 5 h/day, the OR was hardly affected. When subjects who reported >5 h call time/day (38 cases and 22 controls) were excluded altogether, on the premise that such responses were unreliable, the OR decreased to 1.27 (95% CI 0.92–1.75).

Results of sensitivity analyses focusing on the OR for regular use in the past $\geqslant 1$ year are shown in Appendix 1, Table 5 (Supplementary data are available at *IJE* online). All the OR estimates, except two ORs for meningioma relating to the presentation of the study, are well within the 95% CI of the OR from the main analysis.

Discussion

The INTERPHONE study is the largest case–control study of mobile phones and brain tumours conducted to date, including the largest numbers of users with at least 10 years of exposure and the greatest cumulative hours of use of any study. An exhaustive analysis of this large data set involved estimation of hundreds of ORs; rather than focus on the most extreme values, the interpretation should rest on the overall balance of evidence. The null hypothesis of no association would be expected to produce an approximately symmetric pattern of negative and positive log ORs. A skewed distribution could be due to a bias or to a true effect. Our results include not only a disproportionately high number of ORs <1, but also a small number of elevated ORs. This could be taken to indicate an underlying lack of association with mobile phone use, systematic bias from one or more sources, a few random but essentially meaningless increased ORs, or a small effect detectable only in a subset of the data.

For meningioma, there is little evidence to counter a global null hypothesis, and we conclude that INTERPHONE finds no signs of an increased risk of meningioma among users of mobile telephones.

For glioma, an increased OR was seen in analyses in the highest decile of cumulative call time, including tumours in the temporal lobe and subjects who reported having used the mobile phone mainly on the same side as where the tumour occurred. Still, the evidence for an increased risk of glioma among the highest users was inconclusive, as the increase could be due to one or more of the possible sources of error discussed below.

In the following sections, we explore possible explanations for the apparently decreased risk of meningioma and glioma for regular users compared with never regular users, and the apparently increased risk of glioma in a subset of users.

Decreased risk with ever regular use of a mobile phone

An apparently decreased risk of brain tumours with ever regular use of a mobile phone (relative to never regular use) has been seen in other studies.[18,23] Putting aside a genuine protective effect as implausible, we have considered other reasons for these observations.

Sampling bias

In all but two centres, a population-based design was used. This requires that the cases in the study were representative of all cases in the respective population and that the controls represented all non-cases, within matching strata. In practice, it is difficult to demonstrate that these conditions have been fulfilled in any case–control study. Cases may be missed due to lack of detection, misdiagnosis or incomplete registration (such problems may be more likely for meningioma than for glioma). It is uncertain whether the sampling frames used to select controls represented the study base in some countries. To the extent possible, we conducted sensitivity analyses that examined the effects of different recruitment strategies between centres; they did not show substantial changes in the results (Table 6).

Levels of participation

Constrained by the requirements of ethical review committees and facing the population's increasing reluctance to participate in interview studies, we attained participation rates of 78% among meningioma cases, 64% among glioma cases and 53% among controls.[26] Although such proportions are not unusually low, they raise the possibility of selection bias with respect to mobile phone use.

Controls in 11 centres and cases in 9 centres who refused the full interview were asked to respond to a brief non-respondent questionnaire on mobile phone use. The cases and controls who complied with this short inquiry reported a lower lifetime prevalence of ever regular use of a mobile phone than did respondents to the full interview, implying that information from those who participated in the full interview may overestimate prevalence among all eligible subjects. Because participation and refusal differed between cases and controls, such non-representativeness may have distorted the OR estimates.[30] Although caution is required in extrapolating from the findings of the sub-study, we estimated, in the more plausible scenarios, that non-participation bias may have led to a reduction in the ORs for regular use of 5–15%,[30] which is less than the observed reductions below the null in the ORs in ever regular mobile phone users for meningioma (21%, 95% CI 32–9) and glioma (19%, 95% CI 30–6; Table 2).

Prodromal symptoms

Prodromal symptoms of a brain tumour could dissuade subjects from becoming phone users or reduce their use before diagnosis (reverse causation). Glioma is typically diagnosed quite soon after first symptoms. Although prodromal symptoms might result in lowered ORs among very recent users (e.g. <2 years since starting use), these are unlikely to explain the reduction in ORs observed among the vast majority of the users in our study population who started using mobile phones 2–10 years before disease onset.

Timing of interviews

As the use of mobile phones has become more common over time, the later interview dates of controls could have spuriously increased the prevalence of exposure in the control group. However, restricting analyses to matched sets in which the cases and controls were interviewed within 1 month of each other resulted in very little change in the OR for regular use $\geqslant$1 year in the past (Table 6) and hence seems unlikely to explain the low ORs overall. Further, the use of a common reference date for each case and its matched control should have minimized any bias induced by differential timing of interviews.

Confounding

Higher socio-economic status has been associated with a higher risk of brain cancer in some but not all relevant studies,[31,32] and with mobile phone use, particularly when the technology was new.[9] We adjusted for education level in all analyses, but acknowledge this is an imperfect indicator of SES. Otherwise, there are few well-established risk factors for brain tumours; analyses adjusting for measured potential confounders had little impact on the ORs (Appendix 1, Table 4, Supplementary data are available at *IJE* online).

Low overall risks among mobile phone users

The reduced OR for regular users compared with never regular users seems unlikely to reflect a genuine protective effect and makes our results difficult to interpret.[33] It could result from the sources of error discussed above, although based on the evidence we have regarding their magnitude and effects[30,34] they may not account fully for the observed reduction in risk.

It might be possible to correct, at least crudely, for assumed downwards bias in the ORs for mobile phone use by undertaking a series of analyses using the lowest category of users as the reference category for OR estimates in higher categories. Results of such an analysis of the mobile phone use variables in Table 2 are shown in the Table of Appendix 2 (see Supplementary data available at *IJE* online), accompanied by a discussion of the strengths and weaknesses of this approach. We have also done some work to characterize possible sources of bias[30,34] and are currently exploring the possibility of correcting the OR estimates mathematically for their effects.

Elevated risks of glioma among heavy users

There was some evidence of an elevated risk of glioma in the highest decile of cumulative call time, with the highest point estimates seen for tumours in the temporal lobe and for subjects who reported having used their mobile phone mainly on the same side as that on which the tumour occurred. We explore here possible interpretations of these findings.

Biases related to possible differential quality of exposure data

When compared with controls, glioma cases had a higher proportion of proxy respondents, a higher number of imputations for missing values, and a higher proportion of subjects judged by their interviewer to be non-responsive or having poor memory (data not shown). However, sensitivity analyses showed that these differences, on their own, did not explain the results seen in the highest decile of cumulative call time (Table 6).

Differential error between cases and controls in reporting of mobile phone use could substantially affect our results; such information bias could arise from several sources. First, a brain tumour, particularly in the frontal or temporal lobes, may adversely affect cognition and memory.[35] Secondly, cases may be more motivated to recall and report a publicized potential risk factor for their disease.

To investigate the accuracy of self-reported phone use, two validation sub-studies were conducted in some of the INTERPHONE centres. Amongst healthy volunteers using software-modified phones (recording number and times of calls), phone use in the past year was reported with substantial random error; with over- and under-estimation both frequent.[36] Errors were larger for duration of calls than for number of calls, and phone use was under-estimated by light users and over-estimated by heavy users. In another sub-study, records of mobile phone use up to 6 years previously were obtained for some participants in three INTERPHONE centres, allowing us to compare the interview responses with the records.[37] Overall, there was little evidence that recall quality differed between cases and controls, but there was some indication of greater over-reporting by cases than by controls for the period 3–5 years before interview. These sub-studies provide no information regarding differential reporting error for periods more distant than 5 years before interview.

Some subjects reported very high daily average call times and this was more common among cases than controls. Thirty-eight cases and 22 controls reported >5 h use/day and 10 cases and no controls reported $\geqslant$12 h/day. There is reasonable doubt about the credibility of such reports. Excluding all subjects who reported >5 h use/day reduced the ORs in the highest

decile of cumulative time from 1.40 to 1.27 (95% CI 0.92–1.74). In contrast, truncating the average call time to 5 h/day had little effect on the OR. It is not clear which of these two approaches (if either) is more appropriate. However, the key question is whether these cases with unreasonably high values reflect a general tendency for cases to overestimate more than controls, which could contribute to the apparent excess risk in the highest decile. As noted earlier, there is evidence that cases tended to overestimate their past exposure more than controls did.[37]

Non-differential error (random variability or uncertainty in the exposure estimates) may also affect the findings. With dichotomous exposure indicators such bias is towards the null, but for polytomous variables the effect is difficult to predict.[38–40]

Location of tumours and laterality of use of phones

Absorption of RF energy from mobile phones is highly localized.[29] Thus, an association of phone use with tumours occurring near the location of the phone would constitute stronger evidence for aetiology than an association with more distant tumours.

Ipsilateral ORs were almost always greater than contralateral ORs. There was no consistent pattern with regard to level of exposure, although a trend towards a stronger effect of ipsilateral use relative to contralateral use with increasing exposure was observed for cumulative number of calls. Results of case–case analyses (using Inskip's method[18]) also suggested higher risks of gliomas with ipsilateral phone use, but again no consistent trend with increasing exposure. The observation of an unlikely ipsilateral effect in low exposure categories suggests that cases might have over-reported use on the side of the tumour.

There is, though, evidence of lack of such reporting bias from a sub-study. In three centres (Australia, Canada and Japan), participants (172 glioma and 160 meningioma cases and 340 controls who were regular users) were asked at the end of their interview to put a mobile phone to their ear as if answering a call. The concordance between the reported side of use of the phone and the side where it was held was lower for cases (72% glioma cases, 66% meningioma) than controls (95%). The greater degree of concordance among controls suggests differential reporting quality. Among cases, however, there was as much discrepancy in the contralateral direction (52 instances) as in the ipsilateral direction (48 instances). Thus, it is possible that the ipsilateral effect is a true effect, is due to reporting bias or is a mixture of both.

Few studies have related field strength to anatomic structures, but a recent investigation of 110 phone models found that exposure is generally highest in the temporal lobe.[29] While laterality analyses may be biased by the respondent's knowledge of the side of the tumour, results for tumours in different lobes are probably less susceptible to reporting bias. ORs for glioma in the highest exposure categories were higher for tumours in the temporal lobe than in other lobes, but the CIs around the lobe-specific estimates for each measure were wide.

Coherence and consistency

The strongest evidence of an increased risk of glioma was found for cumulative call time, which is a function of the number and duration of calls. Conceptually, cumulative call time might be the most relevant measure of exposure. However, in validation studies, the number of calls was recalled more accurately than the duration of calls.[36,37] For the cumulative number of calls, the ORs, while highest in the highest deciles, were consistently below one. In the absence of a known biological mechanism, it is hard to know whether more weight should be put on results from the more accurate or the conceptually preferred exposure measure.

The apparently increased risk of glioma for cumulative call time was restricted to the top decile, $\geqslant 1640$ h. There was no upward trend across the first nine deciles of cumulative call time. In contrast with the excess risk seen on the scale of cumulative call time, risk did not appear to be increased by length of time since first exposure or by duration of exposure. The pattern of point estimates of ORs in the high call time categories in three strata of time since exposure started—3.8 in the most recent and 1.3 in the more distant ones (Table 3)—is not what one would expect if there were a causal association; although the CI in the newest users was wide and encompassed the point estimates for heavy use in the two longer use groups. By analogy with known carcinogens, the lack of a consistently increasing risk with dose, duration of exposure and time since first exposure weigh against cause and effect. Nevertheless, given the uncertainty surrounding possible effects of RF on the brain, no strong case can be made for the plausibility or implausibility of any observed exposure response pattern.

Comparison of meningioma and glioma results

While the ORs for meningioma were lower than that for glioma in high exposure subgroups, there were some similar patterns. First, the OR for all regular users compared with never regular users was very similar. Secondly, there was no trend in relation to cumulative call time except for an elevated OR in the highest decile. Thirdly, the increase in the last decile was more pronounced for cumulative call time than number of calls. Fourthly, the highest OR for cumulative call time was seen among subjects who had recently started regular use. Fifthly, the ORs were greater for ipsilateral than contralateral use and the ratios of ipsilateral ORs divided by their corresponding contralateral ORs were of a similar

magnitude. However, while there was evidence of a higher risk of gliomas in the temporal lobe than elsewhere with several different exposure metrics, there was no such evidence for meningioma. Although ORs for meningioma were generally lower than that for glioma, the otherwise similar patterns of associations of mobile phone use with meningioma and glioma could indicate shared aetiology or shared bias.

Interpretation of these findings

We have no certain explanation for the overall reduced risk of brain cancer among mobile phone users in this study, although selection bias is almost certainly a contributor. There is some evidence that very high users experienced excess risk of glioma, but that evidence is inconclusive because of possible bias. Further light may be shed on dose–response relations by work now being undertaken with the INTERPHONE data using precise coordinate localization of tumours within the brain in relation to estimates of absorbed RF energy.

The possibility of raised risk in heavy users of mobile phones is an important issue because of their ever-increasing use. Moreover, few subjects in our study had used mobile phones for >12 years; therefore, our results are uninformative with respect to lag periods longer than this.

Consistency with previous research

Our results are consistent with most of the research published to date. A large Danish cohort study of mobile telephone subscribers,[8,9] with an average follow-up time of 8.5 years, found no increased risk of brain tumours in subscribers of $\geqslant$10 years. The first case–control studies conducted included cases diagnosed in the mid-to-late 1990s and therefore could only address possible risks among short-term mobile phone users.[10,12,18,23] In addition, the highest cumulative call times in these studies were much less than in ours. Generally, these studies reported 'negative' results. In contrast, increased risks of malignant brain tumours at higher levels of accumulated use of analogue and digital mobile phones and cordless desktop phones were reported from a sequence of three case–control studies from the same authors with cases in the last diagnosed as late as 2003.[13–15] However, the methods of these studies have been questioned.[41]

Some of the INTERPHONE centres have published their results for brain tumours[11,16,17,19,22,24,25] and two pooled analyses from Northern European centres have also been published.[20,21] Most cases in these reports are included in the present analyses and constitute 69% of gliomas and 57% of meningiomas. The centre-specific analyses are consistent with our all-centre results.

Much biological research has been done in recent years on possible biological effects of RF fields. This work covers *in vitro* and *in vivo* exposure, alone and in combination with other physical or chemical agents, and has found no evidence that RF fields are carcinogenic in laboratory rodents or cause DNA damage in cells in culture.[42] Possible effects of RF fields on other biological endpoints are still being explored.

The possible effects of long-term heavy use of mobile phones on risk of brain tumours require further investigation, given increasing mobile phone use, its extension to children and its penetration worldwide. The problems presented by selection and information bias in this and probably other studies suggest that new studies should, in general, only be done if they can substantially reduce or eliminate selection bias, obtain detailed and high-quality exposure information over the full period of use and offer sufficient statistical power to detect comparatively small effects in people with heavy or long continued exposure. Monitoring of age- and gender-specific incidence rates may also be valuable, particularly if informed by good longitudinal data on mobile phone use by age and sex, and having regard to features such as brain tumour location that may allow more specific inferences about possible mobile phone use effects.

Conclusion

This is the largest study of the risk of brain tumours in relation to mobile phone use conducted to date and it included substantial numbers of subjects who had used mobile phones for $\geqslant$10 years. Overall, no increase in risk of either glioma or meningioma was observed in association with use of mobile phones. There were suggestions of an increased risk of glioma, and much less so meningioma, at the highest exposure levels, for ipsilateral exposures and, for glioma, for tumours in the temporal lobe. However, biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal interpretation.

Supplementary data

Supplementary data are available at *IJE* online.

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KEY MESSAGE

- INTERPHONE is the largest case–control study of mobile phone use and brain tumours yet and includes the largest numbers of users with at least 10 years of exposure. A reduced OR for glioma and meningioma related to ever having been a regular mobile phone user possibly reflects participation bias or other methodological limitations. No elevated OR for glioma or meningioma was observed $\geqslant$10 years after first phone use. There were suggestions of an increased risk of glioma, and much less so meningioma, in the highest decile of cumulative call time, in subjects who reported usual phone use on the same side of the head as their tumour and, for glioma, for tumours in the temporal lobe. Biases and errors limit the strength of the conclusions that can be drawn from these analyses and prevent a causal interpretation.

References

[1] Bernhardt JH, Matthes R, Repacholi MH (eds). Non-thermal effects of RF electromagnetic fields. *Proceedings of the International Seminar on Biological Effects of RF Electromagnetic Fields and Related Health Risks; 1996 Nov 20*. Munich, Germany: International Commission on Non-Ionizing Radiation Protection, 1997.

[2] McKinlay A. Possible health effects related to the use of radiotelephones - recommendations of a European Commission Expert Group. *Radiol Protect Bull* 1997;**187:**9–16.

[3] Repacholi MH. Low-level exposure to radiofrequency electromagnetic fields: health effects and research needs (Review article). *Bioelectromagnetics* 1998;**19:**1–19.

[4] Royal Society of Canada. *A Review of the Potential Health Effects of Radiofrequency Fields from Wireless Telecommunications Devices*. Ottawa: Royal Society of Canada, 1999.

[5] Cardis E, Kilkenny M. International case-control study of cancers of brain and salivary gland - Report of the feasibility study. 99/004. 1999. Lyon: International Agency for Research on Cancer (IARC), IARC Internal Reports.

[6] Cardis E, Kilkenny M. International Case-Control Study of Adult Brain, head and neck tumours: results of the feasibility study. *Rad Prot Dos* 1999;**83:**179–83.

[7] Dreyer NA, Loughlin JE, Rothman KJ. Cause-specific mortality in cellular telephone users. *JAMA* 1999;**282:** 1814–16.

[8] Johansen C, Boice J, Jr, McLaughlin J, Olsen J. Cellular telephones and cancer–a nationwide cohort study in Denmark. *J Natl Cancer Inst* 2001;**93:**203–07.

[9] Schuz J, Jacobsen R, Olsen JH, Boice JD, Jr, McLaughlin JK, Johansen C. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. *J Natl Cancer Inst* 2006;**98:**1707–13.

[10] Auvinen A, Hietanen M, Luukkonen R, Koskela RS. Brain tumors and salivary gland cancers among cellular telephone users. *Epidemiology* 2002;**13:**356–59.

[11] Christensen HC, Schuz J, Kosteljanetz M *et al*. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. *Neurology* 2005;**64:** 1189–95.

[12] Hardell L, Nasman A, Pahlson A, Hallquist A, Hansson MK. Use of cellular telephones and the risk for brain tumours: a case-control study. *Int J Oncol* 1999;**15:**113–16.

[13] Hardell L, Carlberg M, Hansson MK. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997–2003. *Int J Oncol* 2006;**28:**509–18.

[14] Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003. *Int Arch Occup Environ Health* 2006;**79:**630–39.

[15] Hardell L, Mild KH, Carlberg M, Soderqvist F. Tumour risk associated with use of cellular telephones or cordless desktop telephones. *World J Surg Oncol* 2006;**4:**74.

[16] Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren MJ, McKinney PA. Mobile phone use and risk of glioma in adults: case-control study. *Br Med J* 2006;**332:**883–87.

[17] Hours M, Bernard M, Montestrucq L *et al*. [Cell Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study]. *Rev Epidemiol Santé Publique* 2007;**55:**321–32.

[18] Inskip PD, Tarone RE, Hatch EE *et al*. Cellular-telephone use and brain tumors. *N Engl J Med* 2001;**344:**79–86.

[19] Klaeboe L, Blaasaas KG, Tynes T. Use of mobile phones in Norway and risk of intracranial tumours. *Eur J Cancer Prev* 2007;**16:**158–64.

[20] Lahkola A, Auvinen A, Raitanen J *et al*. Mobile phone use and risk of glioma in 5 North European countries. *Int J Cancer* 2007;**120:**1769–75.

[21] Lahkola A, Salminen T, Raitanen J *et al*. Meningioma and mobile phone use – a collaborative case-control study in five North European countries. *Int J Epidemiol* 2008;**37:** 1304–13.

[22] Lonn S, Ahlbom A, Hall P, Feychting M. Long-term mobile phone use and brain tumor risk. *Am J Epidemiol* 2005;**161:**526–35.

[23] Muscat JE, Malkin MG, Thompson S *et al*. Handheld cellular telephone use and risk of brain cancer. *JAMA* 2000; **284:**3001–07.

[24] Schuz J, Bohler E, Berg G *et al*. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone study group, Germany). *Am J Epidemiol* 2006;**163:**512–20.

[25] Takebayashi T, Varsier N, Kikuchi Y *et al*. Mobile phone use, exposure to radiofrequency electromagnetic field, and brain tumour: a case-control study. *Br J Cancer* 2008;**98:**652–59.

[26] Cardis E, Richardson L, Deltour I *et al*. The INTERPHONE Study: design, epidemiological methods, and description of the study population. *Eur J Epidemiol* 2007;**22:**647–64.

[27] Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. *IARC Sci Publ* 1980;**32:**335–38.

[28] Greenland S, Mickey RM. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol* 1989;**130:**1066.

[29] Cardis E, Deltour I, Mann S *et al*. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. *Phys Med Biol* 2008;**53:**2771–83.

[30] Vrijheid M, Richardson L, Armstrong BK *et al*. Quantifying the impact of selection bias caused by non-participation in a case-control study of mobile phone use. *Ann Epidemiol* 2009;**19:**33–41.

[31] Chakrabarti I, Cokburn M, Cozen W, Wang YP, Preston-Martin S. A population-based description of glioblastoma multiforme in Los Angeles County, 1974–1999. *Cancer* 2005;**104:**2798–806.

[32] Schmidt LS, Nielsen H, Schmiedel S, Johansen C. Social inequality and incidence of and survival from tumours of the central nervous system in a population-based study in Denmark, 1994–2003. *Eur J Cancer* 2008;**44:**2050–57.

[33] Saracci R, Pearce N. Commentary: observational studies may conceal a weakly elevated risk under the appearance of consistently reduced risks. *Int J Epidemiol* 2008;**37:** 1313–15.

[34] Vrijheid M, Deltour I, Krewski D, Sanchez M, Cardis E. The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. *J Exp Sci Environ Epidemiol* 2006;**16:**371–84.

[35] Kolb B, Wishaw IQ. *Fundamentals of Neuropsychology*. New York: Worth Publishers, 2008.

[36] Vrijheid M, Cardis E, Armstrong BK *et al*. Validation of short-term recall of mobile phone use for the Interphone Study. *Occup Environ Med* 2006;**63:**237–43.

[37] Vrijheid M, Armstrong BK, Bédard D *et al*. Recall bias in the assessment of exposure to mobile phones. *J Exp Sci Environ Epidemiol* 2009;**19:**369–81.

[38] Birkett NJ. Effect of nondifferential misclassification on estimates of odds ratios with multiple levels of exposure. *Am J Epidemiol* 1992;**136:**356–62.

[39] Brenner H, Loomis D. Varied forms of bias due to nondifferential error in measuring exposure. *Epidemiology* 1994;**5:**510–17.

[40] Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? *Am J Epidemiol* 1990;**132:** 746–48.

[41] Ahlbom A, Feychting M, Green A *et al*. Epidemiologic evidence on mobile phones and tumor risk: a review. *Epidemiology* 2009;**20:**639–52.

[42] SCENIHR. *Health Effects of EMF. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2009*. http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_022.pdf (21 April 2010, date last accessed).

Appendix

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