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To cite this version:

* The Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. International Journal of Epidemiology, 2010, 39 (3), pp.675. 10.1093/ije/DYQ079 . hal-00593672

HAL Id: hal-00593672

https://hal.science/hal-00593672v1

Submitted on 17 May 2011

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OXFORD UNIVERSITY PRESS
International Journal of Epidemiology

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Journal:	*International Journal of Epidemiology*
Manuscript ID:	IJE-2009-05-0410.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	18-Dec-2009
Complete List of Authors:	The INTERPHONE Study Group, *; CREAL
Key Words:	mobile phones, radiofrequency fields, brain tumours

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

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4 December 2009

Word count text: (7129 not including abstract and references)

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SUMMARY

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 10 or more 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).

Odds ratios were below 1.0 for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the tenth decile of recalled cumulative call time, 1640 hours or longer, the odds ratio 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. Odds ratios for glioma tended to be greater in the temporal lobe than in other lobes of the brain, but the confidence intervals around the lobe-specific estimates were wide. Odds ratios 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.

Key words: brain tumours, mobile phones, radiofrequency fields

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INTRODUCTION

Mobile phone use has increased dramatically in many countries since its introduction in the early to-mid 1980's. 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 focusing 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 paper 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.

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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 focused 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 five to 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 two to four 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

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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 6 months or more) (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 histologic type of the tumours. Where possible, location data were obtained from 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 side of 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 paper is used to refer to the 14 analytic entities (12 countries, UK North and UK South). All analyses were carried out for all centres

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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 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 one 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 analyzed 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. 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

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mobile phone use but never as much as one call a week on average for six months or more (about 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 (about 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. Creation of consistent educational levels across the 13 countries is described elsewhere (26). In practice this adjustment had little impact on odds ratio estimates, changing their values by 2% or less in most instances and in all cases by less than 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

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instances, the main analyses in this paper 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. Second, 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 tumor 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. Third, 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

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interviewed three 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.

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RESULTS

During the study period, 3115 meningioma and 4301 glioma cases and 14354 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 Table 1). 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 (about 42%) for meningioma cases, glioma cases and controls.

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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% to 78%). It was higher for glioma cases (62% overall, range: 42% to 80%) and controls (64% overall, range: 45% to 84%), reflecting the different sex distributions of this tumour.

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 around 75 hours, with a median call time of about 2 hours per month and a median lifetime number of calls about 1500. Corresponding values for glioma controls were approximately 100 hours lifetime, 2.5 hours per 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 one year or more in the past, OR 0.79 (95% CI 0.68, 0.91) (Table 2). There was some suggestion of heterogeneity of risk across centres (p=0.08) with ORs below 1.0 except in Canada, Denmark, Germany and Italy (not shown). ORs were below 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 less than 1.0 in the first 9 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

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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 (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 less than 1.0 in all categories of time since start of use, cumulative call time, and cumulative number of calls. Odds ratios for other lobes were also mostly below 1.0 (Table 4).

The odds ratio 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 below 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 (around 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 Table 2) 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). Focusing 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 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 Table 3).

Glioma

A reduced risk of glioma was seen for regular mobile phone use one year or more in the past

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(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 below 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 ≥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 (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 below 1.0) and an increased OR of 1.40 (95% CI 1.03, 1.89) in the highest exposure category, 1640+ hours. Analyses by cumulative number of calls showed ORs below 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 above 1.0 in the highest category (1640+ hours cumulative call time) in each of the three strata. The highest OR was in the short-term users but its confidence interval 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% confidence intervals were wide. Only 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).

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For regular use one year or more in the past, the odds ratio 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 below 1.0 in all categories, except for ipsilateral use beginning 10 or more years in the past (OR 1.21, 95% CI 0.82, 1.80). The ORs by cumulative number of calls were below 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 ORs were all above one with one exception (0.99 for 2-4 years since start of use) and the highest (around 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 Table 2). 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

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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 Table 3).

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 (not shown).

Sensitivity analyses

Selected findings of sensitivity analyses are shown in Table 6 and Appendix Table 4. 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 on 9 cases and 4 controls, fell well within the confidence interval 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 9 cases and 3 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 hours per day, the OR was hardly affected. When subjects who reported over 5 hours call time per 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).

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Results of sensitivity analyses focusing on the OR for regular use one year or more in the past are shown in Appendix Table 5. 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.

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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 odds ratios; 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 odds ratios. A skewed distribution could be due to a bias or to a true effect. Our results include a disproportionately high number of ORs below one, 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

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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). While such proportions are not unusually low, they raise the possibility of selection bias with respect to mobile phone use.

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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). While 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 odds ratios for regular use of 5% to 15% (30), which is less than the observed reductions below the null in the odds ratios 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. While prodromal symptoms might result in lowered ORs among very recent users (eg <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.

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However, restricting analyses to matched sets in which the cases and controls were interviewed within one month of each other resulted in very little change in the OR for regular use one or more years 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 minimised any bias induced by differential timing of interviews.

Confounding

Higher socioeconomic 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 Table 4).

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 odds ratios 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 the Annex, accompanied

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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 odds ratio 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). Second, cases may be more motivated to recall and report a publicised 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

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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 periods 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 more than 5 hours use per day and 10 cases and no controls reported 12 hours or more per day. There is reasonable doubt about the credibility of such reports. Excluding all subjects who reported more than 5 hours use per day reduced the ORs in the highest decile of cumulative time from 1.40 to 1.27 (95% CI 0.92-1.74). By contrast, truncating the average call time to 5 hours per day had little effect on the OR. It is not clear which of these two approaches (if either) is the 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 above, 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).

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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, 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

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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 confidence intervals 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, more than 1640 hours. There was no upward trend across the first nine deciles of cumulative call time. By 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 confidence interval 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

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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 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. Second, there was no trend in relation to cumulative call time except for an elevated OR in the highest decile. Third, the increase in the last decile was more pronounced for cumulative call time than number of calls. Fourth, the highest OR for cumulative call time was seen among subjects who had recently started regular use. Fifth, 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 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

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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 more than 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 10 years or more. 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). The methods of these studies have been questioned, however (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.

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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.

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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 10 or more 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.

KEY MESSAGES

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 odds ratio for glioma and meningioma related to ever having been a regular mobile phone user possibly reflects participation bias or other methodological limitations. No elevated odds ratio for glioma or meningioma was observed 10 or more 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.

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FUNDING

This work was supported by funding from the European Fifth Framework Program, ‘‘Quality of Life and Management of Living Resources’’ [contract QLK4-CT-1999901563] and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers' Forum and GSM Association. Provision of funds to the INTERPHONE study investigators via the UICC was governed by agreements that guaranteed INTERPHONE's complete scientific independence. The terms of these agreements are publicly available at http://www.iarc.fr/en/research-groups/RAD/RCAd.html.

The Australian centre was supported by the Australian National Health and Medical Research Council [EME Grant 219129] with funds originally derived from mobile phone service licence fees; Bruce Armstrong was supported by a University of Sydney Medical Foundation Program Grant and Julianne Brown by an Australian Postgraduate Award. The Cancer Council NSW and The Cancer Council Victoria provided most of the infrastructure for the project in Australia. The Canada-Montréal study was primarily funded by a grant from the Canadian Institutes of Health Research [project MOP-42525]. Additionally, Dr Siemiatycki’s research team was partly funded by the Canada Research Chair programme and by the Guzzo-CRS Chair in Environment and Cancer. Dr Parent had a salary award from the Fonds de la recherche en santé du Québec. The other Canadian centres were supported by a university-industry partnership grant from the Canadian Institutes of Health Research (CIHR), the latter including partial support from the Canadian Wireless Telecommunications Association. The CIHR university-industry partnerships program also includes provisions that ensure complete scientific independence of the investigators. D. Krewski is the NSERC/SSHRC/McLaughlin Chair in Population Health Risk Assessment at the University of Ottawa. The Danish centre was supported by the Danish Cancer Society and the Finnish centre by the Emil Aaltonen

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Foundation and the Academy of Finland. Additional funding for the study in France was provided by l'Association pour la Recherche sur le Cancer (ARC) [Contrat N°5142] and three network operators (Orange, SFR, Bouygues Télécom). The funds provided by the operators represented 5 % of the total cost of the French study and were governed by contracts guaranteeing the complete scientific independence of the investigators. In Germany additional funds were received from the German Mobile Phone Research Program (Deutsches Mobilfunkforschungsprogramm) of the German Federal Ministry for the Environment, Nuclear Safety, and Nature Protection; the Ministry for the Environment and Traffic of the state of Baden-Württemberg; the Ministry for the Environment of the state of North Rhine-Westphalia; the MAIFOR Program (Mainzer Forschungsforderungsprogramm) of the University of Mainz. The study conducted in Japan was fully funded by the Ministry of Internal Affairs and Communications of Japan. In New Zealand, funding was provided by the Health Research Council, Hawkes Bay Medical Research Foundation, the Wellington Medical Research Foundation, the Waikato Medical Research Foundation and the Cancer Society of New Zealand. The Swedish centre was also supported by the Swedish Research Council and the Swedish Cancer Society. Additional funding for the UK-North & UK-South studies was received from the Mobile Telecommunications, Health and Research (MTHR) program and the UK-North study received funding from the Health and Safety Executive, the Department of Health, the UK Network Operators (O2, Orange, T-Mobile, Vodafone, '3') and the Scottish Executive. The Institute of Cancer Research acknowledges NHS funding to the NIHR Biomedical Research Centre.

The views expressed in the publication are those of the authors and not necessarily of the funders.

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ACKNOWLEDGEMENTS

The authors are grateful to Chris Wild (Director, IARC, Lyon, France) for guidance provided to the INTERPHONE Study Group in coming to closure on the final draft of this paper. Special thanks are also due to Peter Inskip (NCI, Bethesda, Md, USA) and Jorn Olsen (Danish Epidemiology Science Centre, Aarhus, Denmark and UCLA, Los Angeles, Ca, USA) for their advice to the Study Group in revising working drafts of the paper. The authors would like to thank Lesley Richardson (Montreal, Canada – formerly at IARC) for her major role in the coordination of the study and assistance in drafting the present manuscript and Dr Baruch Modan (Israel – deceased) for his assistance and enthusiasm in the design and setting up of this study. James Doughty performed miracles implementing the CAPI in several languages and several versions, assisted by Roger Parslow. We would also like to thank Jan Ivar Martinsen for additional programming work. Liz Findlay contributed a great deal to the development of materials and training of interviewers. We would also like to thank all the research assistants and interviewers in the different study centres for their efforts to ensure that the study was carried out with care and with due consideration for the participants.

The Australian team would like to acknowledge the support given to study design and implementation by Associate Professor Michael Besser and Professor Andrew Kaye and the substantial contributions neurosurgery, neuropathology and other clinical staff made to conduct of the study; and to thank the fieldwork staff in Melbourne—Monique Kilkenny, Georgina Marr, Tracey McPhail, Fiona Phillips, Hayley Shaw, Yvonne Torn-Broers; and Sydney—Matthew Carroll, Sally Dunlop, Virginia MacDonald and Elizabeth Willows—and the many interviewers for their hard work, and the NSW and Victorian Cancer Registries for

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aiding case identification. The Canada-Montreal team acknowledges the diligent work of fieldwork staff including Marie-Claire Goulet, Sylvie Plante, Sally Campbell and the interviewer team. We are grateful to Dr. Rafael Glikstein and Dr. Geneviève Matte who contributed to the tumour localisation efforts. The following hospitals and physicians in Montreal permitted access to their patients: Hôpital Charles-Lemoyne (Dr C. Chaâlala, Dr J. Demers, Dr N. Gauthier, Dr A. Roux). Centre hospitalier de l'Université de Montréal (Dr M.W. Bojanowski, Dr A. Bouthillier, Dr J.-J. Dufour, Dr R.A. Moumdjian). Hôpital Maisonneuve-Rosemont (Dr L.N. Poirier, Dr M. Séguin). Hôpital du Sacré-Coeur (Dr J.-F. Giguère, Dr M.F. Giroux). Jewish General Hospital (Dr M. J. Black, Dr. E. Marmor, Dr G. Mohr), Montreal Neurological Institute (Dr R. Del Maestro, Dr A. Olivier, Dr A. Sadikot). The Canada-Ottawa centre gratefully acknowledges the work of the interview team, particularly Lynn Pratt and Daniel Bédard for their leading roles in study coordination; participating clinicians at the Ottawa Hospital included Drs. Charles B. Agbi, Brien Benoit, Martin J. Corsten, Vasco F. DaSilva, André Lamothe, Howard J. Lesiuk, William Miller, Paul F. Odell, and David Schramm. The Canada-Vancouver centre wishes to acknowledge the work carried out by Dr. Alison Pope, Patricia Nelson, Nelson Ha, Dr. Kaushik Bhagat and the interviewer team. We are grateful to Dr. Rafael Glikstein and Dr. Geneviève Matte who contributed to the tumour localisation efforts. The Finnish centre thank Dr J J Jääskeläinen (Helsinki University Hospital), Dr S Valtonen (Turku University Hospital), Professor J Koivukangas (Oulu University Hospital), Professor M Vapalahti (Kuopio University Hospital), Dr T Kuurne (Tampere University Hospital) and Professor R Sankila (Finnish Cancer Registry). We would like to thank the French fieldwork team, Mary-Pierre Herrscher, Fatima Lamri, Agnès Boidart, Hélène Gire, Juliette Krassilchik, Judith Lenti, Delphine Maillac, Frédérique Sonnet, Flore Taguiev, Julie Frantz, France Castay, Florian Gay, for their excellent work; Prof. Doyon (Paris) and Dr. Marc Hermier (Lyon) who were actively

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involved in the both the development of the methodology for tumour localisation and the review of all cases in France; all the hospital services who assisted us in the ascertainment of cases: Lyon - Centre Hospitalier Lyon – Sud (Prof. Dubreuil), Hôpital Neurologique Pierre Wertheimer (Prof. Trouillas, Dr. Honnorat, Prof. Confavreux, Dr. Achiti, Prof. Fisher, Prof. Vallée, Dr.s Farsi and Mahla, Prof. Bret, Dr. Ricci, Prof. Sindou, Prof. Deruty), Hôpital d'instruction des Armées Desgenettes (Dr. Felten), Centre Léon Bérard (Dr. Frappaz), Clinique du Tonkin (Dr. de Garassus, Dr. Brudon) ; Paris - Hôpital de La Pitié Salpétrière (Prof.s Fohanno and Cornu, Dr. Lopes, Dr. Bloch, Dr. Capelle, Dr. Duffau, Prof. Delattre, Dr. Sanson, Prof. Hauw, Prof. Poirier, Dr. Marsault), Hôpital Foch (Prof. Visot, Dr. Gaillard, Dr. Dupuy, Prof. Chabolle), Hôpital Beaujon (Prof. Sterkers, Dr. Bouccara), Hôpital Lariboisière (Prof. Georges, Dr. Blanquet Dr. Koot,, Prof. Tran Ba Huy), Hôpital Ste Anne (Prof. Roux, Dr. Turak), Fondation Rothschild (Dr. Mouder, Dr. Daguet, Dr. Piekarski), Hôpital d'Instruction des Armées du Val de Grâce (Prof. Bequet, Prof. Renard, Prof. Desgeorges) Hôpital St Joseph (Dr. Gauthier), Centre Hospitalier intercommunal de Poissy-St Germain en Laye (Dr. Cambon), Centre Hospitalier Sud-Francilien (Dr. Serre), Centre Hospitalier de Meaux (Dr. Améri) ; Marseille - Hôpital de la Timone (Prof. Peragut, Dr. Regis), as well as all those in the Departments of medical information and all the hospital personnel, particularly the secretaries and the staff in the medical archives, whose assistance proved essential to the success of the project. The German group wish to thank their team members Dr Eva Münster, Marianne Brömmel, Stephanie Estel, Iris Hettinger, Melanie Kaiser, Katharina Kunna-Grass, Klaus Schlaefer, Dr Jürgen Wahrendorf and Anna Wilms and all the interviewers for their skilful work. They thank the clinical Interphone team for their support and collaboration (Bielefeld: Prof Falk Oppel (Neurosurgical clinic), Dr Uwe Dietrich (Neuroradiology), Dr Volkmar Hans (Neuropathology), Heidelberg: Prof Andreas Unterberg, Prof Stefan Kunze, Dr Karsten Geletneky (Neurosurgical clinic), Prof Klaus Sator, Dr Jochen Fiebach

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(Neuroradiology), Prof Marika Kiessling (Neuropathology), Mannheim: Prof Peter Schmiedek, Dr Jochen Tüttenberg (Neurosurgical clinic), Prof Christoph Groden, Dino Podlesek (Neuroradiology), Prof Uwe Bleyl, Dr Rainer Grobholz (Neuropathology), Mainz: Prof Nico Hopf, Dr Dorothee Koch (Neurosurgical clinic), Prof Wolf Mann, Prof Nickalaos Marangos (ENT clinic), Dr Wibke Müller-Forell (Neuroradiology), Prof Hans Hilmar Göbel (Neuropathology)); dedicated to the memory of Prof Axel Perneczky (Neurosurgical clinic). The Israeli center whishes to acknowledge the following neurosurgeons for the help they provided in patients recruitment and ascertainment : Dr. Avi Cohen (Soroka University Medical Center), Prof. Moshe Hadani (Chaim Sheba Medical Center), Prof. Zvi Ram (Tel-Aviv Medical Center), Prof. Zvi Harry Rappaport (Rabin Medical Center), Dr. Sigmund Rothman (Assaf Harofeh Medical Center), Prof. Felix Umansky (Hadassah Hebrew University Medical Center), late prof. George Vaaknin (Tel-Aviv Medical Center), Dr. Uriel Wald (Assuta Hospital) and Prof. Menashe Zaaroor (Rambam Health Care Campus). We are grateful to Dr. Chen Hoffmann and Dr. Dvora Nass (Chaim Sheba Medical Center) who contributed to tumor localization and the review of cases. We acknowledge the diligent work of the fieldwork and office staff including Etti Aviezer, Tehila Ben-Tal, Meirav Dolev, Yonit Deutch, Tamara Rodkin, Ahuva Zultan and the interviewer team. The Italian team (including Prof. Bruno Jandolo, Prof. Paolo Vecchia, Dr. Stefano Martini, Dr. Emanuela Rastelli, Dr. Antonello Vidiri, Dr. Rita Basili, Dr. Caterina Carnovale Scalzo, Dr. Edvina Galiè, Eng. Lucia Ardoino, Eng. Enrica Barbieri, Dr. Cristiano Tesei, Dr. Rossella Rossi, and Massimo Lucibello) dedicates this paper to the memory of Prof. Emanuele Occhipinti, and wishes to thank all the neurosurgeons, ENT-surgeons, neuroradiologists, pathologists, and health managers contributing to the study: Prof. Umberto Agrillo, Dr. Amalia Allocca Dr. Mostafà Amini, Dr. Cinzia Bernardi, Dr. M. Bonamini, Dr. Loredana Bove, Prof. Luigi Bozzao, Dr. Alessandro Bozzao, Dr. Mario Braga, Dr. Fabrizio Breccia, Dr. Velia Bruno, Dr. Andrea

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Brunori, Dr. Antonella Buffoni, Prof. Arnaldo Capelli, Prof. Giampaolo Cantore, Prof. Natale Cantucci, Dr. Emanuela Caroli, Prof. Cosimo Cassano, Dr. Alessandra Castelnuovo, Dr. Costanza Cavuto, Prof. Lucia Cecconi, Dr. Franco Cerquetani, Dr. Carla Colacecchi, Dr. Antonio Comberiati, Dr. Valeria D'Alfonso, Dr. Giovanni De Angelis, Dr. Luca de Campora, Prof. Roberto Delfini, Dr. Carlo Della Rocca, Prof. Marco De Vincentiis, Dr. Domenica Di Stefano, Prof. Stefano Esposito, Prof. Alfredo Fabiano, Dr. Francesco Federico, Prof. Luigi Ferrante, Dr. Anna Rita Fetoni, Dr. Letizia Feudi, Prof. Roberto Filipo, Prof. Roberto Floris, Prof. Felice Giangaspero, Dr. Renato Gigli, Dr. Marco Giordano, Prof. Gianfranco Gualdi, Prof. G. Guglielmi, Dr. Massimo Iachetti, Prof. Giorgio Iannetti, Dr. Maria Rosaria Limiti, Prof. Giulio Maira, Dr. Valentina Manciocco, Dr. Annunziato Mangiola, Dr. Ferdinando Marandino, Dr. Luisa Marangoni, Prof. Pasquale Marano, Prof. Maria Enrica Martini Neri, Dr. Luciano Mastronardi, Dr. Arianna Mattioni, Prof. Maurizio Maurizi, Dr. Maria Concetta Mazzeo, Dr. Giuseppe Natali, Dr. Gaetano Nostro, Prof. Antonio Orlacchio, Prof. Augusto Orlandi, Prof. Fabrizio Ottaviani, Dr. Salvatore Passafaro, Dr. Francesco Saverio Pastore, Dr. Laura Pennesi, Dr. Claudio Maria Pianura, Prof. Roberto Pisa, Dr. Chimene Pistolesi, Prof. Giuseppe Poladas, Dr. Siavash Rahimi, Prof. Antonio Ricci, Dr. Giovanna Ricci, Dr. P. Rigotti, Dr. Massimo Rimatori, Dr. Rossana Romani, Prof. Giuseppe Santeusanio, Dr. Sergio Santilli, Dr. Marco Scarpinati, Dr. Lauro Sciannamea, Prof. Luigi Sinibaldi, Prof. Giuseppe Spriano, Dr. Maurizio Giovanni Vigili, Dr. Massimo Volpe. Moreover, the Italian team is grateful to Dr. Francesco Forastiere, Daniela D'Ippoliti and Stefania Palange (Epidemiologic Unit ASL RME) for their support in case ascertainment from secondary sources and control selection. The collaboration of the Italian mobile phone network operators in providing traffic data for the exposure validation studies is acknowledged. The New Zealand study team acknowledge the assistance and support of the following: the neurosurgeons and support staff at the neurosurgical units at Auckland Hospital (headed by Mr Edward Mee), Wellington

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Hospital (headed by Mr Martin Hunn) and Christchurch Hospital (headed by Mr Martin MacFarlane); the staff at the medical record departments at Auckland Hospital, Wellington Hospital and Christchurch Hospital; the staff at the New Zealand Health Information Service and the New Zealand Cancer Registry; Mr Martin Gledhill at the National Radiation Laboratory; and, the regional coordinators for the study, Ms Cara Marshall, Ms Sue Hawkins and Ms Janfrey Doak. The Swedish centre thanks the Swedish Regional Cancer Registries and the hospital staff; especially the following key persons at the hospitals: Dr J Boethius, Dr O Flodmark, Prof I Langmoen, Dr A Lilja, Dr T Mathiesen, Dr I Olsson Lindblom and Dr H Stibler (Karolinska University Hospital), Dr J Lycke, Dr A Michanek and Prof L Pellettieri (Sahlgrenska University Hospital), Prof T Möller and Prof L Salford (Lund University Hospital), Dr T Bergenheim, Dr L Damber, Prof R Henriksson and Dr B Malmer (Umeå University Hospital). Professor Swerdlow's team in the UK-South included D Hogben, A Butlin, J Owens, A Hart, R Knight, C Parsley, M Pelerin, K Sampson, M Snigorska and M Swanwick. The UK South centre thanks Prof H Møller, Mr B Plewa and Mr S Richards from the Thames Cancer Registry and the following neuropathologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, other health care staff, administrators and secretaries for the help they provided: Mr DG Hardy, Mr PJ Kilpatrick, Mr R Macfarlane (Addenbrooke's Hospital); Ms M Cronin, Ms T Foster, Ms S Furey, Dr MG Glaser, Ms F Jones, Mr ND Mendoza, Prof ES Newlands, Mr KS O'Neill, Mr D Peterson, Ms F Taylor, Prof J van Dellon (Charing Cross Hospital); Dr JJ Bending (Eastbourne District Hospital); Mr PR Bullock, Mr C Chandler, Mr B Chitnavis, Mr L Doey, Mr RW Gullan, Prof CE Polkey, Mr R Selway, Mr MM Sharr, Ms L Smith, Prof AJ Strong, Mr N Thomas (King's College Hospital); Dr GM Sadler (Maidstone Hospital); Dr S Short (Mount Vernon Hospital); Prof S Brandner, Mr G Brookes, Mr AD Cheesman, Professor MJ Gleeson, Miss JP Grieve, Mr WJ

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Harkness, Dr R Kapoor, Mr ND Kitchen, Mrs T Pearce, Mr MP Powell, Dr J Rees, Prof F Scaravilli, Prof DT Thomas, Mr LD Watkins (National Hospital for Neurology and Neurosurgery); Mr AR Aspoas, Mr S Bavetta, Mr JC Benjamin, Mr KM David, Mr JR Pollock, Dr E Sims (Oldchurch Hospital); Mrs J Armstrong, Mr J Akinwunmi, Mr G Critchley, Mr L Gunasekera, Mr C Hardwidge, Mr JS Norris, Dr PE Rose, Mr PH Walter, Mr PJ Ward, Dr M Wilkins (Princess Royal Hospital); Prof TZ Aziz, Prof D Kerr, Mr PJ Teddy (Radcliffe Infirmary); Ms M Allen, Ms T Dale, Mr R Bradford, Dr C Collis, Prof AP Dhillon, Mr NL Dorward, Ms D Farraday-Browne, Dr DJ McLaughlin, Mr RS Maurice-Williams, Dr K Pigott, Ms B Reynolds, Ms C Shah, Mr C Shieff, Dr EM Wilson (Royal Free Hospital); Mr F Afshar, Mr HE Ellamushi, Prof PM Richardson, Mr HI Sabin, Mr J Wadley (Royal London Hospital); Professor M Brada, Dr FH Saran, Mrs D Traish, Mr D Guerrero (Royal Marsden Hospital); Dr S Whitaker (Royal Surrey County Hospital); Dr PN Plowman (St. Bartholomew's Hospital); Mrs Carole Bramwell, Prof A Bell, Mr F Johnston, Mr H Marsh, Mr A Martin, Mr PS Minhas, Miss A Moore, Mr S Stapleton, Dr S Wilson (St. George's Hospital); Dr RP Beaney (St Thomas' Hospital). The UK-North centre wishes to acknowledge the support of the following neuropathologists, neuroradiologists, neurosurgeons, neuro-oncologists, clinical oncologists, neurologists, specialist nurses and administrators based in hospitals located in Scotland (Mr Barlow, Professor I Bone, Ms J Brown, Mr J Crowther, Miss R Dolan, Mr Dunn, Mr MO Fitzpatrick, Mrs M Fraser, Dr R Grant, Dr A Gregor, Mr Johnstone, Mr Lyndsay, Mrs S Macnamara, Miss J Mair, Mr R Mills, Miss Myles, Mr B O'Reilly, Mr V Papanastassiou, Professor R Rampling, Mr Russell, Mr D Sim, Mr P Statham, Mr Steers, Mr Taylor, Prof Teasdale, Professor I Whittle), west Midlands (Dr JM Anderson, Dr Barbour, Dr CR Barraclough, Dr P Bennett, Dr HG Boddie, Mr Brind, Dr Carey, Mr M Choksey, Mr M Christie, Dr RN Corston, Professor GS Cruickshank, Dr A Detta, Mr P Dias, Dr SJ Ellis, Mr G Flint, Dr DA Francis, Mr AH Grubneac, Mr SP

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Harland, Dr C Hawkins, Dr T Heafield, Dr RC Hughes, Dr DG Jamieson , Dr A Logan, Mr CHA Meyer, Mrs R Mitchell, Professor K Morrison, Dr P Newman, Dr D Nicholl, Dr S Nightingale, Dr HS Pall, Mr JR Ponsford, Dr A Shehu, Mr Singh, Dr JA Spillane, Mr P Stanworth, Dr B Summers, Mr AR Walsh, Mr J Wasserberg, Professor AC Williams, Dr J Winer, Mr S Zygmunt), Trent (Dr RJ Abbott, Ms Sheila Adams, Mr Ashpole, Mr RDE Battersby, Professor L Blumhardt, Mr P Byrne, Miss M Cartmil, Dr SC Coley, Dr PCritchley, Dr Faraj, Dr A Gibson, Dr P Griffiths, Dr R Grunwald, Dr TJ Hodgson, Mr DT Hope, Dr S Howell, Dr D Jefferson, Mr D Jellinek, Dr N Jordan, Mr A Kemeny, Dr MC Lawden, Professor J Lowe, Dr N Messios, Ms Kirsty Pardoe, Dr S Price, Dr IF Pye, Mr M Radatz, Mr I Robson, Dr K Robinson, Dr C Romanowski, Dr G Sawle, Dr B Sharrock, Professor P Shaw, Dr C Smith, Dr W Temperley, Dr G Venables, Mr B White, Mr AM Whiteley, Dr Wills) and West Yorkshire (Dr Al-Din, Dr D Ash, Dr J Bamford, Dr M Bond, Dr G Bonsor, Dr L Bridges, Dr B Carey, Dr Chakrabarty, Mr P Chumas, Dr D Dafalla, Dr H Ford, Dr Gerrard, Dr Goulding, Dr J Howe, Dr S Jamieson, Dr Johnson, Dr Louizou, Mr P Marks, Dr M Nelson, Dr S Omer, Mr N Phillips, Mr S Ross, Dr I Rothwell, Dr H Spokes, Dr J Straiton, Mr G Towns, Nr A Tyagi, Mr P Vanhille, Dr M Busby).

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CONFLICTS OF INTEREST

The following potential conflict of interests have been declared.

The Ottawa-Vancouver component of the Interphone study was funded by a university-industry partnerships grant in the amount of $625,000 from the Canadian Institutes for Health Research (CIHR). This is a peer-reviewed federal granting program under which, following successful peer review accordng to the normal CIHR process, funding from the Canadian Wireless Telecommunications Association is matched on a 50% basis by CIHR. Research

conducted under this grant was conducted with no involvement from CWTA; CWTA did serve as a technical resource by providing access to cellular telephone billing records from Interphone subjects in Canada, data on power output levels from base stations, and equipment used by the Ottawa based research team in measuring power output levels from cellular telephones.

The current Chair sponsors are: Afton Chemical Company; American Chemistry Council; European Aluminium Association; Canadian Chemical Produers Association; Canadian Wireless Telecommunications Association; Cerner Corporation; Health Canada; Hydro One; International Aluminium Institute; International Copper Association; R. Samuel McLaughlin Foundation; University of Ottawa.

Professor Armstrong's travel expenses to give an invited lecture were paid by Australian Centre for Radiofrequency Bioeffects Research, which identifies Telstra Australia as a participating institution. This does not represent a conflict of interest with the present submission, but are noted in the interests of full disclosure of RF related work of a commercial nature.

Dr Brown currently owns 426 Telstra shares worth $1452.66 and her husband owns 852 shares worth $2905.32 as of the 10th December 2009.

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Reference List

(1) Bernhardt JH, Matthes R, Repacholi MH, editors. Non-Thermal Effects of RF Electromagnetic Fields Proceedings of the International Seminar on Biological Effects of RF Electromagnetic Fields and Related Health Risks. 96 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. 1999. Ottawa, Royal Society of Canada.

(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; 83:179-183.

(7) Dreyer NA, Loughlin JE, Rothman KJ. Cause-specific mortality in cellular telephone users. JAMA 1999; 282(19):1814-1816.

(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(3):203-207.

(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(23):1707-1713.

(10) Auvinen A, Hietanen M, Luukkonen R, Koskela RS. Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology 2002; 13(3):356-359.

(11) Christensen HC, Schuz J, Kosteljanetz M, Poulsen HS, Boice JD, Jr., McLaughlin JK et al. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. Neurology 2005; 64(7):1189-1195.

(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(1):113-116.

(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(2):509-518.

(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(8):630-639.

(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; 332:883-887.

(17) Hours M, Bernard M., Montestrucq L, Arslan M., Bergeret A, Deltour I et al. [Cell

For Review Only

Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study.]. Rev Epidemiol Santé Publique 2007; 55:321-332.

(18) Inskip PD, Tarone RE, Hatch EE, Wilcosky TC, Shapiro WR, Selker RG et al. Cellular-telephone use and brain tumors. N Engl J Med 2001; 344(2):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(2):158-164.

(20) Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M et al. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer 2007; 120(8):1769-1775.

(21) Lahkola A, Salminen T, Raitanen J, Heinävaara S, Schoemaker MJ, Collatz-Christensen H et al. Meningioma and mobile phone use - a collaborative case-control study in five North European countries. Int J Epidemiol 2008; 37(6):1304-1313.

(22) Lonn S, Ahlbom A, Hall P, Feychting M. Long-term mobile phone use and brain tumor risk. Am J Epidemiol 2005; 161(6):526-535.

(23) Muscat JE, Malkin MG, Thompson S, Shore RE, Stellman SD, McRee D et al. Handheld cellular telephone use and risk of brain cancer. JAMA 2000; 284(23):3001-3007.

(24) Schuz J, Bohler E, Berg G, Schlehofer B, Hettinger I, Schlaefer K et al. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone study group, Germany). Am J Epidemiol 2006; 163(6):512-520.

(25) Takebayashi T, Varsier N, Kikuchi Y, Wake K, Taki M, Watanabe S et al. Mobile phone use, exposure to radiofrequency electromagnetic field, and brain tumour: a case-control study. Br J Cancer 2008; 98(3):652-659.

(26) Cardis E, Richardson L, Deltour I, Armstrong B, Feychting M, Johansen C et al. The INTERPHONE Study: Design, Epidemiological Methods, and Description of the Study Population. Eur J Epidemiol 2007; 22(9):647-664.

(27) Breslow NE, Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. IARC Sci Publ 1980;(32):5-338.

(28) Greenland S, Mickey RM. The impact of confounder selection criteria on effect estimation. Am J Epidemiol 1989; 130(6):1066.

(29) Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, Varsier N et al. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 2008; 53(11):2771-2783.

(30) Vrijheid M, Richardson L, Armstrong BK, Auvinen A, Berg G, Carroll M et al. Quantifying the impact of selection bias caused by nonparticipation in a case-control study of mobile phone use. Ann Epidemiol 2009; 19(1):33-41.

(31) Chakrabarti I, Cokburn M, Cozen W, Wang YP, Preston-Martin S. A population-

For Review Only

based description of glioblastoma multiforme in Los Angeles County, 1974-1999. Cancer 2005; 104:2798-2806.

(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(14):2050-2057.

(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(6):1313-1315.

(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. Journal of Exposure Science and Environmental Epidemiology 2006; 16(4):371-384.

(35) Kolb B, Wishaw IQ. Fundamentals of Neuropsychology. New York: Worth Publishers, 2008.

(36) Vrijheid M, Cardis E, Armstrong BK, Auvinen A, Berg G, Blaasaas KG et al. Validation of short-term recall of mobile phone use for the Interphone Study. Occupation Environment Medicine 2006; 63:237-243.

(37) Vrijheid M, Armstrong BK, Bédard D, Brown J, Deltour I, Iavarone I et al. Recall bias in the assessment of exposure to mobile phones. J Exp Sci Environ Epidemiol 2009; 19(4):369-381.

(38) Birkett NJ. Effect of nondifferential misclassification on estimates of odds ratios with multiple levels of exposure. Am J Epidemiol 1992; 136(3):356-362.

(39) Brenner H, Loomis D. Varied forms of bias due to nondifferential error in measuring exposure. Epidemiology 1994; 5(5):510-517.

(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; 132:746-748.

(41) Ahlbom A, Feychting M, Green A, Kheifets L, Savitz DA, Swerdlow AJ et al. Epidemiologic evidence on mobile phones and tumor risk: a review. Epidemiology 2009; 20(5):639-652.

(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

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

Characteristics of the study population	Meningioma N	%	Glioma n	%
All interviewed cases	2425	100	2765	100
Cases included in main analysis[2]	**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 at diagnosis	316	13	635	23
Aged 40-49 at diagnosis	806	33	841	31
Aged 50-59 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

[1]The controls for each case series have the same distributions of characteristics as the cases to which they are matched.

[2]Excluded are cases for whom no controls could be found (55 for glioma and 15 for meningioma) and cases in matched sets (2 for glioma and 1 for meningioma) where the regular use status of the case or the control was unknown.

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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[1]	95 % CI		Cases	Controls	OR[1]	95 % CI	
Regular use 1 or more years in the past										
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 years	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	0.67	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 (hours)[2]										
Never regular user	1147	1174	1.00			1042	1078	1.00		
<5 hours	160	197	0.90	0.69	1.18	141	197	0.70	0.52	0.94
5.0-12.9	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)[2]										
Never regular user	1147	1174	1.00			1042	1078	1.00		
<1.5 x 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

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

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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				
Cumulative Call time (hours)	Cases	Controls	OR[1]	95% CI		Cases	Controls	OR[1]	95% CI	
	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 hours	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 hours	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 hours	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

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

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Table 4 – ORs between mobile phone use and brain tumours (meningioma and glioma separately) by anatomical location of tumor[1] 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													
	Tumor in temporal lobe					Tumor in parietal or frontal lobes					Tumor in other locations					Tumor in temporal lobe					Tumor in parietal or frontal lobes					Tumor in other locations				
	Cases	Cont-rols	OR[2]	95% CI		Cases	Cont-rols	OR[2]	95% CI		Cases	Cont-rols	OR[2]	95% CI		Cases	Cont-rols	OR[2]	95% CI		Cases	Cont-rols	OR[2]	95% CI		Cases	Cont-rols	OR[2]	95% CI	
Regular use 1 or more years in the past																													
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 years	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 (hours)[3]																													
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 hours	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)[3]																													
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 x 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

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[1] 115 gliomas and 357 meningiomas with unknown anatomical location are not included

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

[3] 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.

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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[1]

	Meningioma											Glioma										
	Ipsilateral phone use					Contralateral phone use					Ratio[3] ipsi/ contra	Ipsilateral phone use					Contralateral phone use					Ratio[3] ipsi/ contra
	Cases	Cont-rols	OR[2]	95 % CI		Cases	Cont-rols	OR[2]	95 % CI			Cases	Cont-rols	OR[2]	95 % CI		Cases	Cont-rols	OR[2]	95 % CI		
Regular use 1 or more years in the past																						
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 reg. 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 (hours)[4]																						
Not reg. user	821	898	1.00			832	841	1.00				773	838	1.00			721	718	1.00			
<5 hours	48	71	0.76	0.48	1.21	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
5.0-114.9	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)[4]																						
Not reg. user	821	898	1.00			832	841	1.00				773	838	1.00			721	718	1.00			
<1.5 x 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

[1] 72 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 paper 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

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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.

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

[3] Ratio of OR for ipsilateral tumours to OR for contralateral tumours

[4] 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.

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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[1]	95 % CI		Cases	Controls	OR[1]	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[2]	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[3]	116	97	1.09	0.76	1.56	201	139	1.50	1.10	2.06
Balanced interviewer workload[4]	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[5]										
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 hours per day[6]	130	107	1.15	0.81	1.62	208	153	1.38	1.02	1.87
Truncation of phone use to 1 hour per day[6]	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[7]	136	117	1.08	0.78	1.51	225	167	1.31	0.98	1.75
Exclusion of subjects who reported more than 5 hours per day[6]	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

[1] ORs adjusted for sex, age, study centre, ethnicity in Israel, and education.
[2] Japan and France-Paris excluded
[3] Included only interviewers who conducted at least 20 interviews
[4] Included only interviewers' whose case/control interview ratio was between 1/4 and 3/4 (between 1/6 and 5/6 in Germany where 2 controls were matched to each case)

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[5] 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.
[6] Truncation and exclusion were based on all use of a mobile phone; that is, including when using hands-free devices
[7] Working days were assumed to be 5.5 days a week for 50 weeks of the year and new deciles were created to reflect the changed total hours.

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