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Mobile Phones, Brain Tumours and the Interphone Study:

Where Are We Now?

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Abbreviations: CI = confidence interval; OR = odds ratio; RF = radiofrequency; SAR = specific (energy) absorption rate
Abstract

Background
In the past 15 years, mobile phone use has evolved from an uncommon activity to one with over 4.6 billion subscriptions worldwide. There is, however, public concern about the possibility that mobile phones might cause cancer, especially brain tumours.

Objectives
To review the evidence on whether mobile phone use raises risk of the main types of brain tumour, glioma and meningioma, with a particular focus on the recent publication of the largest epidemiological study yet – the 13-country Interphone Study.

Discussion
Methodological deficits limit the conclusions that can be drawn from Interphone, but its results, along with those from other epidemiological, biological and animal studies, and brain tumour incidence trends, suggest that within about 10-15 years after first use of mobile phones there is unlikely to be a material increase in the risk of brain tumours in adults. Data for childhood tumours and for periods beyond 15 years are currently lacking.

Conclusions
Although there remains some uncertainty, the trend in the accumulating evidence is increasingly against the hypothesis that mobile phone use can cause brain tumours in adults.
Introduction

In just 15 years the mobile phone has evolved from an uncommon, expensive, brick-shaped object used in restricted areas of Western countries to a convenient and ubiquitous part of modern life, with more than 4.6 billion subscriptions worldwide (International Telecommunication Union 2010). The arrival of this mass technology has been accompanied by some public and media concern about the possibility that the radiofrequency (RF) fields emitted by the phones might cause cancer, especially brain tumours. Numerous committees have considered the evidence and recommended more research (IEGMP 2000; SCENIHR 2009). Since 1999, a series of epidemiological studies of mobile phone use and cancer have been published, mainly focused on brain tumour risks. Collectively, they have not provided evidence of a relationship, but they have had sufficient limitations to leave the question unresolved (Ahlbom et al. 2009).

The Interphone study was launched in 2000, to provide a more powerful and methodologically rigorous investigation of this issue by collecting data in 13 countries. Now, 10 years and €19M later, after much anticipation and a lengthy delay, the key results on brain tumours have been published (INTERPHONE Study Group 2010). What should be made of them, considered along with the rest of the literature? Do we now know whether mobile phones cause brain tumours? Or if not, how much closer are we to knowing?
The Interphone Study

The Interphone study was an international, coordinated interview case-control study, investigating the potential effect of mobile phone use on the risk of the two commonest types of brain tumour, glioma and meningioma (and, although not yet published, also acoustic neuromas and parotid gland tumours). It used a common core questionnaire and to some extent a common core protocol, but deviations and additions were allowed: for instance, cases were population-based in most countries but hospital-based in Japan and France, and controls were pair matched at 9 centres but stratum matched in the other 7. These methodological inconsistencies add to the difficulty of interpreting the overall results. Nevertheless, the multicentre structure enabled a study of exceptional size: more than 5,000 patients with these relatively uncommon tumours were interviewed in a five year period – a considerable feat.

The study questionnaire asked in detail about the type and pattern of use of each mobile phone the respondent had used, and about other RF exposures and brain tumour risk factors. The questionnaire was administered by an interviewer using a computerised laptop data entry system (except in Finland), with practical advantages but with the disadvantage that there were no original paper records available to check the fidelity of data entry for apparently erroneous values. The questionnaire collected information on hands-free phone use, which was excluded from analyses since head exposure is then negligible. It is unknown, however, how well subjects can recall past use of hands-free devices, and whether recall differed between cases and controls.
The analyses employed post hoc matching of one control per case (two for Germany) for the centres that had used a stratified control selection. Individually matched analyses were then used for the analyses. This resulted in loss of data: 70 cases and over 2000 interviewed controls were not included in the final analyses. Furthermore, most of the national studies that contributed to Interphone covered a wider age-range (as low as 18 and/or up to 69) than the Interphone analyses (30-59), so that a considerable proportion of the national data (e.g., 58% for Sweden (Lonn et al. 2005)), were not included in the overall pooled analyses. The national publications need to be considered, therefore, as additional semi-independent sources of evidence, not simply as subsets of the overall Interphone analysis.

The Interphone publication (INTERPHONE Study Group 2010) compared 2708 glioma cases diagnosed at ages 30-59 years during 2000-2004, with 2972 controls, and 2409 meningioma cases with 2662 controls. Participation rates were 64% for glioma cases, 78% for meningioma cases, and 53% for controls, with considerable variation among study centres; proxies were used for 13% of glioma cases, 2% of meningioma cases and 1% of controls. Sensitivity analyses did not suggest, however, that the results were dependent on participation rates across centres or on inclusion of proxies.

Key findings were a significantly diminished risk of both glioma and meningioma in regular users compared with people who were not users or were occasional users (“non-users”); no trend in risk of either tumour type with cumulative hours of use but an apparent raised risk of glioma, and to a lesser extent meningioma, in those in the top decile of cumulative hours of use; and no relation of risk of either tumour type to
cumulative number of calls, years of use or years since first use. These results raise several important issues:-

**Reduced Risk of Brain Tumours in Mobile Phone Users**

The Interphone Study, as well as some previous case-control studies (Inskip et al. 2001; Muscat et al. 2000) and the only large cohort study (Schuz et al. 2006), identified a reduced risk of brain tumours among mobile phone users compared with non-users. In the Interphone study as a whole, ever-regular use was associated with an odds ratio of 0.79 (0.68-0.91) for meningioma, and 0.81 (0.70-0.94) for glioma. The pattern was consistent across the Interphone study sites and statistically precise, calling for explanation.

There is empirical evidence that the reduced risks were in part due to non-response bias (Vrijheid et al. 2009). Cases and controls who initially declined to participate but agreed to complete a short non-response questionnaire had lower frequencies of regular mobile phone use than those who participated fully. The quantitative results from this non-response questionnaire imply that selection bias would produce an odds ratio of 0.87-0.92 if the null hypothesis were true. It seems unlikely that differential response based on mobile phone use could explain the diminished risk entirely since the reduction in risk was similar for study centres that did and did not reveal to potential participants the study’s focus on mobile phone use.

Even if the same pattern of diminished response by non-users occurred for cases and controls, which it did not, the overall greater non-participation among controls due to
refusal would result in a downward bias in the odds ratio. Whereas only 11% of glioma and meningioma cases refused to participate, 30% of controls did so. Furthermore, the phone use of those who did not complete even the non-response questionnaire (e.g. because of refusal or death) is unknown, adding further uncertainty to the extent of the overall bias.

Other likely contributors to the diminished ORs in users are prodromal symptoms such as headaches and impaired cognition, which may have prevented recent initiation of mobile phone use among subjects with as yet undiagnosed brain tumours. Thus some cases who would otherwise have become short term users may have remained non-users, leading to artefactually reduced odds ratios for brain tumour in phone users, especially short term users (and low cumulative users, since short term use will tend to result in low cumulative use). It seems likely that this accounts for at least part of the decreased risk in users because the strongest reduction in glioma risk was found in the shortest term users. Other potential contributors to diminished ORs can be hypothesised, but there is no evidence for them (see Supplemental Material, page 1).

The appropriate analytic approach and interpretation in the light of this presumably non-causal reduction in risk is not obvious. One suggested response has been to alter the referent group, by using low regular use rather than non-use plus occasional use as the referent. This results in an upward shift in the odds ratios across the board, more for glioma than meningioma, but no change in the magnitude of those odds ratios relative to one another across the range of exposure (INTERPHONE Study Group 2010). However, whether this decreases or increases the bias is dependent on two
factors—whether the diminished risk is due to non-response, and whether the biases apply also to low level users as well as non-users. Neither of these factors is known, but to the extent that the diminished risk is due to prodromal symptoms, changing the referent group would produce upward bias. If short term users (or low cumulative users) are used as the referent exposure group, the more pronounced risk reduction in this group caused by prodromal symptoms would make relative risks for long term users (or high cumulative users) biased upward.

Risks after prolonged and heavy mobile phone use

If exposure to RF fields through mobile phone use were tumourigenic, people using mobile phones longest and those who were the heaviest users would be expected to show the highest risks of brain tumours. Reliability of recall of amount of use a decade ago is unknown, and the average amount of use is likely to have shifted over time as phone use has escalated universally. Validation studies of recall of phone use in the last six months, and up to approximately 5 years in the past, have found that even in the short term, subjects on average underestimate the number of calls per month but overestimate duration of calls, with moderate systematic error (underestimation by light users, overestimation by heavy users) and a large amount of random error (Vrijheid et al. 2006). Recall of number of calls was found to be better than recall of their duration. Furthermore cases in Interphone more often than controls gave implausibly high estimates of overall time spent on calls (e.g., 10 cases and no controls reported average use of >12 hours/day). A validation study including both cases and controls found that there was overestimation by cases in more distant time periods that could cause positive bias in risk estimates (Vrijheid et al. 2009). It thus
appears that recall of amount of use was appreciably erroneous and quite likely
different for cases than controls. It is possible that recall of year of first use, and
hence duration of use, may have been more reliable than recall of amount of use.

Notwithstanding the inherent unreliability of recalled amount of use, the only
cumulative mobile phone exposure measures available in Interphone were duration
and amount. Neither yielded material evidence of a positive association with brain
tumours. Specifically, for the longest-term users (10+ years since first use), no
association was seen for glioma (OR 0.98 (95% CI 0.76–1.26)), or meningioma (OR
0.83 (95% CI 0.61–1.14)). Most ORs were <1.0 and no dose-response pattern was
seen. This is consistent with results from a cohort study based on subscriber lists
(Schuz et al. 2006) but in contrast with the raised risks for long-term use reported by
Hardell et al (Hardell et al. 2006a; Hardell et al. 2006b). For heavy use measured by
estimated total number of calls, again there was no positive association with brain
tumours: ORs were <1.0 in all categories of numbers of calls, including those in the
top decile, for both glioma and meningioma. For heavy use assessed by cumulative
duration of calls, again there was no dose-response effect for either type of tumour.
For glioma, while the risk estimate for subjects in the highest decile of total call-time
(≥1640 hours) was modestly raised at OR 1.40 (95% CI 1.03–1.89), it was disjointed
from the risk in the next heaviest users, the second highest decile, which was one of
the lowest risk estimates: OR 0.71 (95% CI 0.53-0.96). Similarly for meningioma the
OR in the highest decile of total call-time OR was 1.15 (95% CI 0.81–1.62), while in
the next heaviest decile of users it was 0.76 (95% CI 0.54-1.08). Furthermore, the top
‘decile’ category presented was not actually 10% of the control data – it is unknown
to what extent risk would have been raised in the true top decile, or to what extent the
raised risk is a function of the cut-point chosen (about the 7th centile for menigioma, and the 8th centile for glioma).

The only previously available risk estimates among comparably heavy users are from case-control studies conducted by Hardell et al (2006a, 2006b) in Sweden, who reported a markedly raised risk and positive dose-response gradient for “malignant tumours” but not for menigioma. We have discussed elsewhere why the Hardell results are problematic (Ahlbom et al. 2009). Assessment of the findings with respect to cumulative call time in individual published component studies of Interphone, whose participants variously covered a wider range of ages than Interphone, confirmed the lack of dose-response effect with glioma (see Supplemental Material, page 2). Furthermore, for number of calls, which validation studies suggest may be better-reported than cumulative hours of exposure, there was no indication of raised risk in the top decile or of dose-response.

Finally, participants who had been using mobile phones the longest (>10 years) and had accumulated highest lifetime call hours (≥1640 hours) might be expected a priori to have been at the highest risk if RF exposure were tumourigenic. This was not the case however for either glioma (OR 1.34 (95% CI 0.90-2.01)) or menigioma (OR 0.95 (95% CI 0.56-1.63)) (INTERPHONE Study Group, 2010). Instead it appeared that the very few individuals who started regular use only 1-4 years ago, yet whose cumulative call time fell in the highest decile, due to their reported recent heavy use, carried the greatest risk of both tumour types: for glioma OR 3.77 (1.25-11.4) and for menigioma OR 4.80 (1.49-15.4), with no dose-response. The similarity of the results for menigioma and glioma suggests that shared recall bias exists, since such a short-
term usage period should have little or no bearing on the pathogenesis of meningioma, which tends to have a long latent period.

The magnitudes of relative risk of glioma and meningioma found in the top decile of cumulative use of phones were not large (1.40 and 1.15, respectively), and are on the margins of what epidemiology can detect. It is at a level at which the errors and biases identified in the study data provide a plausible, indeed at present a more plausible, alternative explanation of the findings than does causation. Furthermore the analyses were derived from a very large number of comparisons investigated (some reported in the paper, the great majority not), and hence there was the potential for selective emphasis in presentation of the results.

In summary, Interphone and the literature overall have methodological deficiencies but do not demonstrate greater risk of either glioma or meningioma with longer or greater use of mobile phones, although the longest period since first use examined is <15 years.

Anatomical distribution of the tumours compared with anatomical distribution of exposure

RF exposure during mobile phone use is highly attenuated within a few centimetres in the brain, and therefore exposure is largely to the side of the brain, and to the anatomical area, closest to the antenna. It has been reported that on the side of the brain where the phone is used, 50-60% of the total RF energy is absorbed in the temporal lobe and the average specific absorption rate (SAR) is highest in the
temporal lobe and the cerebellum (Cardis et al. 2008). Thus examination of location of the tumour in relation to location of exposure is of interest.

*Laterality*

If there were a causal association between mobile phone use and brain tumour risk, one would expect an increased risk on the same side of the head as the phone is held, and a null finding on the opposite side. On the other hand, if some brain tumour patients believed that mobile phone use had caused their tumour, and consequently over-reported use on the affected side, this would result in an apparent risk increase on the same side of the head accompanied by a decreased risk on the opposite side. (The same bias is not possible for controls, who do not have a tumour side). Furthermore, if there were a causal relationship, one would expect an effect of laterality to occur after a sufficient induction period, not for solely recent use (unless there were a very rapid and substantial promotional effect of mobile phones, which presumably would be detectable easily and rapidly from population incidence trends).

ORs for glioma and meningioma in the Interphone study 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 for most categories of duration of use, cumulative call time and cumulative number of calls. Most ipsilateral ORs were not above unity, however, and there was no dose-response trend, although the greatest ORs tended to be for the top decile of ipsilateral exposure.
There are currently no validation studies of retrospective self-reported side of use, and there is no evidence of consistency over time in the preferred side of use. Overall, the greater risk for reported ipsilateral than contralateral use would be compatible with causation or bias as an explanation, but the finding that contralateral risks and many of the ipsilateral risks were generally below unity, with no consistent pattern of greater ipsilateral/contralateral ratios with greater exposure (except for cumulative number of calls and risk of glioma), would favour bias as the explanation.

*Lobe*

The risk of glioma in the temporal lobe for regular use and for most categories of exposure was reduced and not different from that in other lobes. ORs for long term use and highest cumulative call time, however, were somewhat greater in the temporal lobe than in other lobes: this is the pattern one would expect if there were a causal effect, although there was no suggestion of a dose-response effect for temporal tumours, which would also be expected if there were causality. No coherent pattern was observed for meningioma, for which the OR for temporal lobe tumours for regular use was somewhat lower than for other lobes and there was no evidence of greater risk in the temporal than other lobes in other categories of use.

*Exact anatomical location of the tumour*

Interphone collected neuroradiological information on the exact locations of brain tumours in the study. Although this has not been published for the study overall, it has been published for glioma for many of the study centres and meningioma for one.
centre. These analyses gave no indication of an association of tumour risk to proximity of the tumour to the exposure source (Larjavaara et al., 2011; Takebayashi et al. 2008).

In summary, among the three types of data on anatomical location, the results for laterality of phone use are the least interpretable. They are compatible with bias, or at least partly with causation, but do not give firm evidence for either. The evidence on lobe of glioma, but not of meningioma, is inconsistently in the direction that would be expected with causality, but not decisively so. The evidence on exact location of the tumour, which one would expect to give the most rigorous analysis since it has greater precision without bias, does not support a causal association.

Data on tumour risk in relation to type of mobile phone, and hence of exposure, have not suggested a relation (Supplemental Material, page 2).

Other relevant evidence

The biological literature on RF and cancer does not support an aetiological effect - extensive research has not established any biological mechanism by which radiofrequency fields, which are not mutagenic, could cause cancer, and animal experiments have given no replicable evidence for cancer causation in animals (SCENIHR 2009).

The major biases and uncertainties in interpretation of the Interphone study are similar to those in other interview-based case-control studies of brain tumours and mobile phones. The exceptional size of the Interphone study has not proved to be a critical
strength – issues of bias and misclassification have proved far more important than
tightness of confidence intervals. Therefore, more studies of the same basic design as
Interphone, based on recall of phone use, no matter how carefully designed and
conducted are unlikely to add materially to our knowledge. There are other
epidemiological designs that do not share these weaknesses (although they have
others), whose results need consideration in relation to the uncertainties remaining
after Interphone: studies of the effects of occupational and residential RF exposures;
record linkage-based case-control and cohort studies of phone use; and trend analyses
of brain tumour incidence rates in the general population.

The occupational studies, and those of cancer risk in relation to residential proximity
to RF broadcasting towers, have not indicated any cancer risk although they have
been methodologically weak (Ahlbom et al., 2004). Studies that have linked private
non-corporate telephone subscription records to cancer registry records (in certain
Nordic countries) (Auvinen et al., 2002; Schuz et al., 2006) or death records (in the
US) (Dreyer et al., 1999) have the strengths that they avoid recall bias and
misclassification, and avoid participation bias. They have the weaknesses, however,
not present in interview case-control studies such as Interphone, that the subscription
data exclude corporate subscriptions, which in the early years were likely often to
have been held by heavy users, and that the named subscriber is not necessarily the
user. These problems are likely to have diluted any true association. A US cohort
study (Dreyer et al.1999) was halted one year after recruitment, so was essentially
uninformative. A national records-based case-control study in Finland (Auvinen et al.
2002) based on very short durations of use found a borderline significantly raised risk
of glioma in ever-users with some evidence for a relation to analogue not digital
phone use. A Danish cohort study (Schuz et al. 2006) followed 420,000 phone
subscribers over a period of 7-21 years and gave no indication of raised risk of glioma
or meningioma nor any trend in risk with duration since first use.

Analyses of secular trends in brain tumour incidence, in countries that have had good
quality diagnostic facilities and cancer registration, can give powerful evidence
constraining what can reasonably be proposed as an aetiological relationship. The
dramatic rise in mobile phone use over a relatively short period of time provides an
unusual opportunity to assess the potential for a causal effect on cancer occurrence
through high quality, unbiased descriptive epidemiological data. As substantial
misclassification is inevitable in recall-based exposure information from the
Interphone interviews, it follows that if the raised relative risk observed in the top
decile of users in the Interphone study were causally due to phone use, not chance or
artefact, then the true effect would likely be much larger, and therefore more easily
detectable in population cancer incidence trends. However, data from the Nordic
countries 1974-2003 (Deltour et al, 2009), children in the Nordic Countries 1985-
1987-2007 (Kohler et al, 2011) showed no indication of increases in brain tumour
incidence in relation to the introduction and growing use of mobile phones, up to 20
years after their introduction and 10 years after their use became widespread.
This does not appear compatible with the greatest risk shown in the Interphone study – the odds ratios of about 4 within 5 years of first use for individuals using a phone for ≥1,640 hours cumulatively, nor with the risk estimates using a ‘low user’ baseline group, in the Appendix of the Interphone paper.

The Interphone levels of exposure were those in the population in 2003 and earlier, since when prevalence and probably levels of use have increased greatly. Future examination of cancer incidence trend data over the next few years, especially by age of occurrence and anatomical location of tumours, should greatly clarify whether mobile phones cause brain tumours: if there are no apparent effects on trends in the next few years, after almost universal exposure to mobile phones in Western countries, it will become increasingly implausible that there is a material causal effect. Conversely, if there are unexplained rising trends, there will be a case to answer. Supplemental Material Figure 1 shows the most recently available data, up to 2009, from Sweden, one of the earliest adopters of mobile phones; the data give evidence against an impact of mobile phone use on brain tumour occurrence.

**Conclusions**

Interphone is an impressively large study with multiple indices of exposure. However, it has some methodological deficits, largely inevitable in recall-based case-control studies, which limit interpretation of its findings. Such evidence as it provides, combined with the results of biological and animal studies, other epidemiological studies, and brain tumour incidence trends, suggest that within the first 10-15 years after first mobile phone use there is unlikely to be a material increase in risk of adult
brain tumours resulting from mobile phone use. At present there are no data on risk of childhood tumours.

The deficiencies of exposure measurement, because of recall misclassification in studies such as Interphone, and because of mis-identification of users in records-based studies such as the published cohorts, leave it doubtful that either study type could reliably detect a small effect, if one existed. Both for this reason, and because research cannot in principle prove the complete absence of an effect, but only place limits on its possible magnitude, there is bound to remain some uncertainty for many years to come. The limited duration of data yet available, which is mainly for up to 10 years of exposure and to a lesser extent for a few years beyond this, also leave uncertainty because of the potential for long lag period effects, especially for meningioma which is generally slower growing than glioma. The possibility of a small or a longer term effect thus cannot be ruled out. Nevertheless, while one cannot be certain, the trend in the accumulating evidence is increasingly against the hypothesis that mobile phone use causes brain tumours.
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