

Commentary: Call me on my mobile phone...or better not?—a look at the INTERPHONE study results

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Mobile phone (cell phone) use is increasing extraordinarily rapidly worldwide. There are now 4.6 billion mobile phone subscribers worldwide.¹ In many low- and middle-income countries use of cell phones has made communications possible in vast areas lacking cable connections. Increasingly, in high-income countries, cell phones have replaced 'land lines' for personal telecommunications. Users of mobile phones are exposed to electromagnetic radiation, which has long been hypothesized to have adverse health effects, including increased risk of cancer.^{2,3} Research on biological mechanisms of cellular and tissue injury by electromagnetic radiation has been inconclusive, and consequently epidemiological studies have been the principal source of evidence on potential health risks of mobile phone use. Brain tumours have been of particular concern because the electromagnetic radiation generated by mobile phones passes through the brain when the phones are used without a hands-free device. To date, findings of diverse studies on mobile phone use and brain tumour risk have been reported with mixed findings, but with no clear indication of increased risk for cancer.^{4,5} To provide needed evidence on the potential risk of brain cancer associated with mobile phone use, the International Agency for Research on Cancer (IARC) initiated a multi-centre case-control study, the INTERPHONE study, in 1998–99.

A much awaited report from this large international study on mobile phone use and brain tumours is published in this issue of the *IJE*.⁶ A number of previous papers cited in the article reported only partial findings from components of the multicentre study, heightening expectations on what the full data set would eventually show. The component studies were relatively underpowered, but they exhibited a rather consistent and baffling *reduced* risk among cell phone

users. We now have the complete results and the researchers' interpretation of them. The INTERPHONE investigators conclude that 'There were suggestions of an increased risk of glioma, and much less of 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 conclusion we can draw from these analyses and prevent a causal interpretation'.⁶ This statement, as with a similar one ('...these biases and errors prevent a causal interpretation of the results.') at the end of the Appendix 2 of the article⁶ added during the editorial process of revision, is both elegant and oracular. Similar to any oracle it tolerates diametrically opposite readings. If more weight is given to the first sentence, a conclusion is reached in favour of an increased risk, albeit not definitively manifest yet, from intensive use of mobile phones. Giving more weight to the second sentence leads to the conclusion that there are enough sources of errors in the study to dismiss the apparent elevated risks as not real. With equal weight to the two sentences, any conclusion hangs in the balance.

Is there any way out of this ambivalence? INTERPHONE is the largest study yet carried out and published on mobile phone use and cancer. It includes 2409 cases of meningioma, 2708 cases of glioma and two series of, respectively, 2662 and 2972 controls matched by age, sex and region of residence. With the coordination of IARC it has mobilized investigators in multiple centres within 13 countries '... to determine whether mobile phone use increases the risk of [brain] tumours and, specifically, whether radiofrequency energy emitted by mobile phones is tumorigenic'.⁶

Certainly this is the question that scientists, people and public health decision-makers have in mind, as

they seek assurance that mobile phone use is safe and not a cause of brain tumours. As defined by Lowrance,⁷ 'a thing is safe if its risks are judged to be acceptable'. This definition implies a need for quantification of risk, the role of epidemiological research and a judgement of its acceptability in individual and societal contexts. The risk of main interest is lifelong use, possibly beginning in childhood—a pattern of exposure that cannot yet be studied. The now testable scientific question and that addressed by the INTERPHONE study is whether mobile phones increase the risk of brain tumours within the first 10–15 years of use, a question much less liable to generate unwarranted expectations about the evidence that the INTERPHONE study could actually deliver. In high-income countries, mobile phone use began in the 1980s but was not widely prevalent until the mid-1990s. The cancer cases in the study were diagnosed between 2000 and 2004. As a consequence, <5% (110/2409) of the meningioma cases and <9% (252/2972) of the glioma cases occurred >10 years since start of mobile phone use. None of the today's established carcinogens, including tobacco, could have been firmly identified as increasing risk in the first 10 years or so since first exposure. Ionizing radiation is a recognized cause of brain tumours but except for rare instances the radiation induced cases occur on average after 10–20 years since the time of first exposure. INTERPHONE shares with all studies previously carried out on mobile phones and cancer the inherent limitation that it can investigate only a short period of observation since first exposure; the distribution of exposure is brief and truncated leaving limited incubation time for an exposure-related cancer to develop. Hence observing no increase in risk would be reassuring but only to a limited extent.

As a multi-centric study, INTERPHONE has, however, the potential advantage of incorporating simultaneous replication, if there is no methodological heterogeneity across the centres. Consistency of results among centres, a key element for drawing causal inferences, can be immediately examined, rather than awaiting the accumulation of results from successive and separate studies. Overall, a consistent inter-country pattern of replicated reduced risk for both meningioma and glioma is shown in Table 6 of Appendix 1 of the INTERPHONE article⁶, whereas Table 2 of the article shows an equally consistent pattern of reduced risks for different metrics of exposure (regular use vs never regular use, cumulative call time, cumulative number of calls) with only three odds ratios (ORs) out of 50 above 1. These results are also in line with the detailed findings already published in separate reports, involving nearly half of the cancer cases, from some of the participating countries. On the null hypothesis that there is no association between mobile phone use and brain cancer, ORs fluctuating randomly above and below 1 would be

expected, whereas the observed patterns of reduced risks, on average of the order of 30%, would have a tiny probability of occurring just by chance. Having ruled out chance and the possibility of a protective effect—absent any supporting biological evidence—less plausible than the possibility of bias from a variety of sources, bias stands as the most likely explanation of the observed results. As already noted,⁸ this interpretation carries the uncomfortable consequence that the interpretation of *any* result of the study becomes problematic, unless the sources of bias are identified and their consequences quantified.

The authors have carefully pursued bias as an explanation of their findings via several routes. Confronted with a participation rate appreciably lower among controls (average for centres: 53%) than among cases (averages of 78% for meningioma and 64% for glioma), they asked a sample of participants (cases in 9 centres, controls in 11 centres) who had refused the full interview to respond to a brief questionnaire. Among both cases and controls, non-participants reported a lower lifetime prevalence of mobile phone use than participants. Since the participation rate among controls was lower than among cases, this pattern of response to the request for participation introduces a lower frequency of regular phone users among controls than among cases. Extrapolating the findings from this sample to the whole study population, the researchers estimated^{6,9} that this selective non-participation bias may have led to a reduction in the ORs for regular use of 5–15%, potentially accounting for most of the bias observed (Table 2 of the article⁶) for meningioma [21%, 95% confidence interval (CI) 9–32] and glioma (19%, 95% CI 6–30). A substantiated downward and generalized bias implies that any observed increase in risk would be underestimated, independent of statistical significance. If this bias extends to those with the highest exposure, then an increased risk has been observed in spite of this downward bias. In the top decile of cumulative call time, the most comprehensive metric of exposure, the observed and probably underestimated ORs are 1.15 for meningioma and 1.40 for glioma (Table 2 of the article⁶). People in the top decile used a mobile phone for a total of ≥ 1640 h, still not a very intensive use by today's pattern: spread over 10 years, the lower limit of this category is about half an hour per day. Sensitivity analyses (bottom part of Table 4 of Appendix 1 of the article⁶) show that the increased ORs are fairly consistent among countries. They appear further increased (Table 5: 1.45 for meningioma and 1.96 for glioma) when the participant reported using the phone on the same side of the tumour, yet the systematically higher ORs for ipsilateral vs contralateral use, even at low levels of exposure, points to reporting bias and casts doubt on this latter result.

A second approach to bias investigation and correction is presented in Appendix 2 of the INTERPHONE

article⁶. To avoid the problem of a lower frequency of regular users among controls (arising from non-participation), ORs were calculated taking the lowest levels of regular use as the reference category rather than non-regular use. This approach has been often employed in occupational epidemiology when risk is compared between people at various level of exposure rather than between exposed and non-exposed subjects, the latter being regarded as an entirely different group. The table in Appendix 2 of the article⁶ shows that the ORs for meningioma are only slightly changed (cf. Table 2 of the article⁶), whereas those for gliomas are now mostly close to (and above) 1; the OR for the top decile of cumulative call time has increased from 1.40 to 1.82. The direction of these corrections, the size of which may be questionable (as discussed in Appendix 2 of the article⁶) speaks again in favour of a contribution of non-participation bias to the observed low ORs. A further reason for the downward bias may, however, lie in a different direction, briefly mentioned in Appendix 2 of the article⁶. Low risks have been a recurrent feature not only of the INTERPHONE study, but also of other studies of mobile phones and brain tumours, including a nationwide cohort study¹⁰ in which non-participation was not an issue. Major clinical manifestations of brain tumours may not be long lasting but lesser symptoms, including occasional seizures, may develop over several years before diagnosis, as indicated by findings of increased risk of brain tumours in people with a hospital discharge diagnosis of epilepsy ≥ 8 years earlier, the risk progressively increasing as the interval between epilepsy and tumour diagnosis becomes shorter.¹¹ In addition, a nationwide cohort study using the same database as the cohort brain cancer investigation¹² found reduced hospitalization rates among mobile phone users for a variety of central nervous system diagnoses (Alzheimer's disease, vascular dementia, other dementia, Parkinson's disease and epilepsy) for time periods up to 10 years after starting phone use. One explanation is that mobile phone users may be a healthy group showing a 'healthy user effect' but a more likely one is that people with prodromal manifestations of neurological disease make less use of mobile phones. Along with non-participation this selection bias may also contribute to the downward bias in the INTERPHONE study.

We commend the INTERPHONE investigators for a rigorously implemented protocol and the careful exploration of bias. INTERPHONE clearly demonstrates that epidemiological research has to give major emphasis to bias prevention and control. For the time being, INTERPHONE's findings, interpreted in the context of prior studies, tells us that the question as to whether mobile phone use increases risk for brain cancers remains open. Given the relatively short time of observation since first exposure and the acknowledged biases we simply do not know the answer to this question. Some may interpret the results

differently and most who have been awaiting the results of the INTERPHONE study will be disappointed by its mixed findings. Those upholding a precautionary approach to the extent and manner of use of mobile phones may find some support in the elevated risks noted in subjects with the highest exposures.

Not surprisingly, we end by calling for more research, given the increasingly ubiquitous use of mobile phones, rising use by children and the indication from some studies, including the INTERPHONE study, that mobile phone use may increase risk for brain tumours. One possibility to minimize selection and information biases, proposed previously by Rothman,¹³ would track cohorts of mobile phone users with exposures documented via company records and outcomes ascertained through record linkage with cancer registries. Large cohorts would be required to investigate adult brain cancers that have an incidence rate in the order of 10 per 100 000 person-years but the advantage is that once established a cohort can be repeatedly followed up in time, updating exposure measurements in cases and a random control sample. This type of investigation overcomes the problem of case-control studies conducted when not enough time has elapsed since first exposure to make possible the emergence of long latency adverse health effects. This approach was blocked in the USA through litigation.¹⁴ Another possibility would be periodic replication of multi-centric case-control studies, comparable with the INTERPHONE study in design, although the potential for bias would likely remain.

Fortunately, high-quality cancer registries are in place in many countries around the world and descriptive patterns of brain tumour occurrence can be monitored through careful and ongoing analyses to detect changes suggestive of increased risk from mobile phone use.

The tired refrain 'more research is needed' fully applies in this instance: without more research the public's question about the acceptability of cancer risk from mobile phones will remain unanswered.

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