Indications of possible brain-tumour risk in mobile-phone studies: should we be concerned?

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Indications of possible brain-tumour risk in mobile-phone studies: should we be concerned?

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Mobile-phone use has increased dramatically in most countries since its introduction in the early to-mid 1980s. The expanding use of this technology has been accompanied by concerns about health and safety. In the late 1990s, several expert groups critically reviewed the evidence on health effects of low-level exposure to radiofrequency (RF) electromagnetic fields, and recommended research into the possible adverse health effects of mobile telephone use.[1–4] As a result, a number of studies have been conducted,[5–14] including a large 13-country collaborative study, Interphone, with over 2700 glioma and 2400 meningioma cases and their matched controls, which was recently published.[15]

Studies on the health effects of mobile phones are very complex, and interpretation of the results necessitates understanding and careful consideration of various aspects including the timing of the study, the exposure variables of relevance and the influence of methodological limitations. Indeed, the results of studies to date, in particular those of the recently published Interphone international analyses,[15] have been interpreted differently by various groups: some have taken them to suggest that mobile phones are safe, others that they cause tumours, while some have suggested that the limitations of the studies were such that no conclusion could be drawn.

This editorial discusses the main issues in the interpretation of the findings reported in recently published studies of brain tumours in relation to mobile-phone use, particularly the largest of these, Interphone, and their potential public-health implications.

TIMING OF THE STUDY

Most published studies to date have found no increased risk (and in many instances even a decreased risk) associated with ever having used a mobile telephone. These studies, however, were conducted at a time when mobile communication was still a relatively new phenomenon with low levels of use compared with today. As an illustration, though the largest study, Interphone, started in 2000, the maximum duration of use among the study participants was about 12 years, and only 5 years had passed from the start of heavier use. For most known carcinogens, however, identification of increased risk of solid tumours (particularly brain tumours) has required long follow-up periods of subjects with substantial exposure. For example, while the atomic bombs were dropped on Hiroshima and Nagasaki in August 1945, an excess risk of solid tumours was reported in the survivors only in the 1960s, and no elevation in risk of brain tumours was noted for about 50 years.[16 17]

The decision to conduct epidemiological studies of brain tumours in relation to mobile phones under these circumstances was based on the urgency of data regarding possible health effects of this widespread technology and the possibility that the effect of exposure could be seen relatively early after exposure based on the hypothesis that RF might act in the later stages of carcinogenesis.[2 3 18]

Although no firm conclusion can be drawn at present, owing to methodological limitations, several studies have found suggestions of an increased risk of brain tumours in relatively long-term users.[11 19–21] In Interphone, no such increase was seen in the main analyses; however, in a subanalysis where short-term users (instead of never users) were used as the reference category, an increased risk was seen among long-term users, with an indication of a trend for increasing risk with increasing time since start of use.[22]

EXPOSURE VARIABLES OF RELEVANCE

Risk, if it exists, is expected to be found in categories that reflect a higher exposure, that is among long-term and/or heavy users and in tumours in the most exposed regions of the brain.

In all studies published to date, the exposure distribution was very skewed, and most mobile-phone users were low users compared with today. For example, in the Interphone study, the median cumulative call time over life was around 100 h, and the median call time 2–2.5 h per month. Even the highest decile of cumulative call time (1640 h or more), if spread over 10 years, corresponded to only about 27 min of phone use per day. Thus, if a risk exists, it will be diluted in analyses of 'ever use' or 'ever regular use' of mobile phones. Analyses by level of use (in terms of amount and duration) are therefore essential in order to evaluate whether a risk exists.

Such analyses have been conducted in most published studies. In the Interphone study, although no increased risk was seen for ever having been a regular mobile-phone user (actually a reduced risk was observed), a 40% increase in risk was seen for glioma in the highest decile of cumulative call time. This observation could reflect recall bias, with cases overestimating their duration of use in the highest category of use, as there was no indication of an exposure–response relationship in lower deciles. It could also reflect a genuine risk among heavy users, while the lack of exposure–response could be due to the relatively narrow exposure range spanned by the lower deciles, which may not allow discrimination of an exposure–response relationship. Thus, although we would not expect a major overall increase in risk of brain tumours due to the relatively low level of use which characterises most published studies to date, observations in the highest-exposed group are particularly important, as this could be a sentinel group, signalling effects that might be found in studies with higher and more relevant exposure patterns.

Another important issue is that exposure from mobile phones is very localised: most of the RF energy (97–99% depending on frequency) is absorbed in the brain hemisphere on the side of the head where the phone is used (ipsilateral), mainly in the temporal lobe, and decreases rapidly

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with increasing depth.[23] The risk, if it exists, is therefore likely to be confined only to a small proportion of the entire brain. Thus, analyses of all brain tumours together are also likely to dilute the risk.

The findings in several studies of an increased risk for glioma among the highest users on the side of the head where the phone was used[11 15 24–26] and, in Interphone, in the temporal lobe[15] are therefore important. These are the findings that would be expected if there was a risk, as these are the a priori relevant exposure variables.

INFLUENCE OF METHODOLOGICAL LIMITATIONS

Similar to other epidemiological studies, a number of biases affect the results of case–control studies of mobile phones, including Interphone, in particular, the growing problem of high refusal rates among population controls and potential differential recall between cases and controls.

The observations of an overall reduced risk among regular users in several studies[13–15] and the fact that most of the risk estimates are below 1 in the Interphone study[15] indicate a potential selection bias. This is confirmed, in the later study, by the observation of high refusal rates among controls and results of non-response questionnaires that suggest that non-users may have been under-represented in the study, particularly among controls. If this is the case, all of the ORs in this study may have been underestimated. Although it is difficult to quantify this precisely, different plausible scenarios investigated by Vrijheid and collaborators indicate that the underestimation could be by a factor of 5 to 20%.[27]

One approach for compensating for potential selection bias is the conduct of users only analyses, excluding unexposed subjects. This approach has been widely used in occupational epidemiological studies. It has been recommended in the presence of dissimilarity between exposed and unexposed subjects, such as differences in refusal rates, or in the presence of an important confounder distinguishing users and non-users.[28 29] This method was applied to the Interphone data, resulting in ORs above 1 for glioma, but not meningioma, with indications of an increased risk with increasing duration of use, as well as among the heaviest users.[22]

The observation, in many studies, of increased ORs on the side of the head where the phone was used among long-term or heavy users could be a real effect of mobile phones on glioma development or an artefact of differential recall between cases and controls often seen in case–control studies. In Interphone, a number of different analyses address the issue of laterality recall bias. A substudy in which subjects were handed a telephone at the end of the interview to verify the reported side of phone use indicated that cases were as likely to misreport phone use on both the ipsi- and contralateral sides of the head. This argues against a laterality recall bias. Case-only analyses indicated an increased risk among ever regular users, and analyses in which the ratios of ipsi to contralateral ORs were considered showed high ratios among short-term and low users, suggesting a possible recall bias. Apart from these low use categories, however, the ratios tended to increase with time since start of use, with cumulative call time and with numbers of calls, suggesting a true effect of mobile-phone use. Taken together, these results suggest that the ipsilateral effect may be a mixture of bias and a true effect.

The observation of an increased OR in the highest decile of cumulative call time in the temporal lobe (the anatomical region of the brain with the highest amount of absorbed RF energy) is also relevant to this interpretation. While laterality is a subjective variable reported by subjects who might tend to over-report using mobile phones on the side of the head where their tumour is located, anatomical location is an objective parameter obtained from clinical records. This observation, therefore, also provides support for a genuine effect, as does the fact that sensitivity analyses conducted to evaluate the robustness of the findings generally showed similar results.

It is not possible to evaluate the magnitude and direction of the different possible biases on the study results and to estimate the net effect of mobile phones on the risk of brain tumours. The overall balance of the above-mentioned arguments, however, suggests the existence of a possible association.

While more studies are needed to confirm or refute these results, indications of an increased risk in high- and long-term users from Interphone and other studies are of concern. There are now more than 4 billion people, including children, using mobile phones. Even a small risk at the individual level could eventually result in a considerable number of tumours and become an important public-health issue. Simple and low-cost measures, such as the use of text messages, hands-free kits and/or the loud-speaker mode of the phone could substantially reduce exposure to the brain from mobile phones. Therefore, until definitive scientific answers are available, the adoption of such precautions, particularly among young people, is advisable.

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