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Paper: Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study. Interphone Study Group. International Journal of Epidemiology 2010; 1–20. doi:10.1093/ije/dyq079.

Introduction:

The rapid increase in the use of mobile telecommunications has raised questions about whether exposure to the radiofrequency (RF) signals from mobile telephones, with their antennas located close to the head when making a call, could be associated with an increase in the incidence of head and neck cancers.

Following a recommendation for more research from the International Electromagnetic Fields (EMF) Project of the World Health Organization (WHO), the International Agency for Research on Cancer (IARC), a WHO specialized agency on cancer, coordinated an international epidemiological study in 13 countries (16 centres) using the same core protocol.

Countries participating in the study were: Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Interphone consists of a set of interview-based case-control studies focusing on four types of tumours in tissues that most absorb radiofrequency (RF) energy emitted by mobile phones (brain, meninges, acoustic nerve and parotid gland). A thorough description of the study design, the epidemiological methods and the population available for the international analyses was published a few years ago [Cardis et al., 2007].

Results of national analyses of the relation between mobile phone use and risk of specific tumour types in some of the participating countries have been published, including two studies from Japan (Christensen et al 2004, 2005; Hartikka et al., 2009; Hepworth et al, 2006; Hours et al, 2007; Klaeboe et al, 2007; Lönn et al, 2004, 2005, 2006; Sadetzki et al, 2007; Schlehofer et al, 2007; Schoemaker et al, 2006; Schüz et al, 2006; Takebayashi et al, 2006, 2008). Pooled analyses of data from Northern European countries and the UK on mobile phone use and risks of glioma and meningioma have also been published (Lahkola et al, 2007; 2008). Now results for all countries and centres for gliomas and meningiomas have been published (The Interphone Study Group, 2010). The Interphone study is the largest and most comprehensive epidemiological study conducted to date on mobile phone use and brain tumours, and contains the largest number of long-term phone users.

Methods:

Eligible for inclusion in the Interphone brain tumours study were all new cases of glioma and meningioma at ages 30-59 years diagnosed in the study regions between 2000 and 2004, totalling 4301 glioma and 3115 meningioma cases. Cases were actively ascertained

within all neurological facilities in the study regions, and completeness of ascertainment was checked through population- or hospital-based cancer registries, medical archives, and hospital discharge or billing files. All diagnoses were histologically confirmed or based on unequivocal diagnostic imaging. One or two controls per case were selected from a population source that varied by country. Controls were either individually or frequency matched by age, sex and region.

When combining all countries, interviews were completed for 2425 meningioma cases (78% of total identified), 2765 glioma cases (64% of total identified) and 7658 controls (53% of those asked to participate). Slightly smaller numbers of cases and controls were included in the individually matched international analyses. Ratios of case- to control-participation rates varied across countries, between 1.03 and 2.19 in the meningioma study and from 0.75 to 2.00 in the glioma study.

The main 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).

Information was collected on past mobile phone use during face-to-face computer assisted interviews (CAPI). If the case died before interview, or was too sick to answer questions, a proxy was interviewed. Among glioma cases 13% of interviews were based on proxy respondents; these numbers were much smaller for meningioma cases (2%) and controls (1%).

Exposure to mobile phone RF signals was determined by how often and for how long the phone was used. For example, “regular users” were those who made at least one call per week for a period of 6 months or more. These were compared to a group who did not use mobile phone regularly (defined as “never regular use”) or did not use them at all. An allowance was made for a latency of 1 year and cumulative use was reduced if the subject reported use of a hands free device.

In calculating cumulative times of phone use missing information for selected periods of time was replaced with imputed values based on adjacent periods; 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. Approximately 65 % of glioma cases and 68 % of glioma controls used a mobile phone regularly. The numbers were 57 % for meningioma cases and corresponding number for controls was 62 %.

Information was also collected on other exposures to RF fields, ionizing radiation, medical history, educational level (as a surrogate for socio-economic status), occupation and smoking.

Due to the localization of exposure to RF fields emitted by mobile phone during voice calls, the spatial distribution of specific absorption rates (SAR) within the brain is highly inhomogeneous. On the side of a brain where the phone is used, most (50-60%) of the

total RF energy is absorbed in the temporal lobe and the average relative SAR is highest in the temporal lobe and the cerebellum (Cardis et al., 2008). To account for tumour location, the lobe of the brain in which the tumour occurred was determined and each control was assigned the anatomical site of the tumour of the matched case.

The side of the head that the user recalled to be the predominant side for phone use was asked at interview. 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 location. Laterality was not assigned if the subject reported switching the side on which the phone was used or if the tumour crossed the midline of the brain.

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 years after first phone use (glioma: OR 0.98; 95% CI 0.76–1.26; meningioma: OR 0.83; 95% CI 0.61–1.14). ORs were <1.0 for all deciles of lifetime number of phone calls and nine deciles of cumulative call time. In the 10^{th} decile of recalled cumulative call time, ≥1640 h, the OR was 1.40 (95% CI 1.03–1.89) for glioma, and 1.15 (95% CI 0.81–1.62) for meningioma; but there were implausible values of reported use in this group. ORs for glioma tended to be greater in the temporal lobe than in other lobes of the brain, but the CIs around the lobe-specific estimates were wide. ORs for glioma tended to be greater in subjects who reported usual phone use on the same side of the head as their tumour than on the opposite side.

Difficulties in Interpretation:

Interphone reports effect estimates below unity in analyses of mobile phone use and brain tumour risk, especially for short term mobile phone use, which if true would imply a protective effect. However, the investigators believe this is implausible and discuss other possible explanations, such as biases, for the apparently reduced risks.

1. Selection bias

A case-control study relying on self-reported mobile phone use is dependent on the willingness of cases and controls to participate in the study. There has been a tendency of decreasing participation rates world-wide during the past decade. Generally, cases are more willing to participate as they are often more interested in research aiming at finding causes to their disease. If willingness to participate is related both to the disease and to the studied exposure, selection bias might be introduced by non-participation. In the Interphone study, participation rates varied considerably between study centres, and a non-responder questionnaire was used to assess the impact of non-participation on risk estimates (Vrijheid et al., 2009_a). Both among cases and controls, mobile phone users were more willing to participate, and earlier regular users were more willing to participate than more recent users. This was particularly problematic for controls, whose

participation rates were lower. It was estimated that selection bias would reduce risk estimates by approximately 5-15%, which explains some, but not all of the risk reduction.

On the other hand, if participation bias were the main reason for the reduced odds ratios, the reduction would be expected to be less in study centres with less unbalanced participation rates of cases and controls. Counter to this, there was no correlation between the centre-specific ORs for glioma and meningioma among regular users *vs* not-regular users and the local ratio of case- to control-participation rates (Appendix 1, Table 6).

Moreover, within each local centre, the ratios of case- to control-participation rates in the glioma and meningioma studies were quite similar (Appendix 1, Table 6). Hence, it is not clear why the reductions in the ORs for glioma in the lowest exposure categories are much greater than those for meningioma; for example (Table 2), the OR for glioma at 1-1.9 years since first use is 0.62 (95% CI 0.46-0.81) while that for meningioma is 0.90 (95% CI 0.68-1.18) and each point estimate is not within the 95% confidence interval of the other. The contrast is similar but not as great for the lowest categories of cumulative call-time and number of calls.

For this same reason, it is also difficult to understand why the analyses restricted to regular users only (Appendix 2) provided such diverging results for the glioma and the meningioma studies; in these analyses the ORs for glioma were mostly above the null in all categories of times since start of use, cumulative call time and cumulative number of calls, while persisting and widespread deficits for meningioma risk were observed.

2. Prodromal symptoms

Based on the arguments above, alternative explanations were sought for the observed risk reductions among regular users. There is a possibility that brain tumour patients, because of prodromal symptoms, might have been less likely to take on a new technology during the last few years prior to their tumour being diagnosed. As mobile phone use was increasing rapidly in the rest of the population, the proportion of mobile phone users would be lower among brain tumour patients compared to the general population, because the cases are less likely to adopt mobile phone use, resulting in reversed causality.

Glioma is believed to be a rapidly growing tumour that manifests itself in a short period of time, while progression of meningioma to overt clinical disease is considered comparatively slower. However, there is evidence of prodromal symptoms being present several years prior to glioma diagnosis in a study of the association between epilepsy and brain tumours (Schwartzbaum et al., 2005). Epilepsy was more prevalent between both low-grade and high-grade glioma cases than controls, up to 8 years prior to glioma diagnosis. A similar association was also seen for meningioma, but considerably weaker.

If people with an undiagnosed brain tumour are affected by the disease in a way that makes them less likely to start using a mobile phone in the period preceding diagnosis or to use it less intensively than healthy people of comparable age and gender, the risk

estimate for mobile phone use will be reduced due to a phenomenon of reverse causation. Moreover, if prodromal symptoms made glioma cases less likely than meningioma cases to take up regular mobile phone use close to the time of diagnosis of the tumour, this could explain the greater risk reduction observed in the lowest exposure categories for glioma than for meningioma.

3. Exposure misclassification

All studies based on phone use are affected by exposure misclassification. Exposure assessment in Interphone was based on self-reported information: on duration and amount of mobile phone use provided during an interview. Compared to mobile phone use inferred from subscriber status and date of first subscription, more relevant and detailed data about levels of mobile phone use can be collected when information is obtained directly from the participants. However, self-reported data may be subject to recall and reporting bias. Validation studies have shown that both healthy individuals and brain tumour patients have a tendency to overestimate the length of their calls and to underestimate the frequency (Vrijheid, et al. 2006; Vrijheid, et al. 2009$_b$), and that heavy users tend to overestimate, whereas light users underestimate their use. In addition, the exposure validation study investigating reliability of recall among a subsample of cases and controls over a period of approximately four years provided evidence that cases tended to overestimate their past exposure more than controls (Vrijheid, et al. 2009$_b$). However, there are currently no data available on quality of recall for periods of time longer than 5 years, and there is also a lack of data on recall of time since first mobile phone use.

It is likely that non-differential exposure misclassification is present in Interphone. Should there be a true effect of exposure on the risk of disease, with dichotomous exposure indicators, the direction of such bias is towards the null, but for variables with several levels the effect is more difficult to predict. If there is no true association between the exposure and the disease, non-differential exposure misclassification will not affect the risk estimates, i.e. risk estimates will be close to unity anyway. The differential recall among cases and controls (recall bias), i.e. the tendency for cases to overestimate exposure for more distant time periods, would lead to a positive bias (over-estimation of the risk), which could result in spurious associations.

Moreover, some subjects classified in the top decile (10%) of cumulative call time reported very high daily average call times, and this was more common among cases than controls (in the glioma study, 38 cases and 22 controls reported more than 5 h use/day and 10 cases and no controls reported over 12 h/day). There is reasonable doubt about the credibility of such reports. Based on traffic data recorded by network operators, no subjects in both the Interphone exposure validation studies (Vrijheid, et al. 2006; Vrijheid, et al. 2009$_b$) actually used the phone for more than 70-80 minutes per day. Excluding all subjects who reported >5 h use/day reduced the OR for glioma in the highest decile of cumulative time from 1.40 to 1.27 (95% CI 0.92–1.74). When these implausible values were reduced but still assigned to the highest category the OR did not change.

4. Laterality analyses

RF exposure during mobile phone use is highly localized and penetrates only a few centimetres into the brain. Therefore, mobile phone use on one side of the head is not expected to affect tumour risk on the other side. In Interphone the question was asked about the habitual side of the head the mobile phone was used. Separate analyses were made of the association between tumour risk and mobile phone use on the same (ipsilateral) and opposite (contralateral) side of the head. There are currently no validation studies of the retrospective self-reported side of use, and there is no evidence of consistency over time in the preferred side of use. Retrospective self-report of preferred side of use might be subject to bias. If cases believe that mobile phone use may have caused their tumour they might over-report mobile phone use on the same side as the tumour. This would not be the case for controls who, at the time of interview, did not know which side of the head they will be assigned in the analyses for the tumour location. Should there be 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 believe that mobile phone use has caused their tumour, and over-report use on the affected side, this would result in an apparent risk increase on the same side of the head accompanied with a decreased risk on the opposite side.

Discussion:

The Interphone study represent a new generation of studies on possible risks related to mobile telephony, which provided new information on this rapidly growing and already extremely prevalent exposure. Among the strengths are large and carefully planned international efforts with emphasis on case definition and ascertainment, exposure assessment and quality control. Nevertheless, important limitations remain. Exposure assessment relies on self-reported mobile phone use and therefore is susceptible to recall bias. Selection bias may be introduced due to differential participation rates among cases and controls, and among exposed and non-exposed. In almost all centres participating subjects appear to be more likely to be phone users and participation rates are higher in cases compared to controls; an indication of selection bias. Estimates of selection bias in the validation study suggest a reduction of the risk by 5-15%. However, there is a consistent reduced risk of about 20% reported in most of the analyses. Moreover, the reductions in glioma and meningioma risks in the international analyses did not appear to be driven by centres attaining the lower participation rates among controls or the higher differential participation of cases and controls. Thus, a phenomenon of reverse causality, stemming from a reduced propensity for cases not to start using mobile phone during the prodromic phase of their disease, could also contribute to explaining these findings. There are also limitations regarding the length of the latency period that can be studied for this new exposure and this study did not include children.

Conclusions:

A reduced risk was observed in the majority of analyses – likely reflecting bias. When cumulative call times were analysed among recent, medium and long-term phone users there was no indication of any excess risk of meningiomas or gliomas except for glioma

in the highest cumulative call time category, but there was no dose-response. Due to numerous biases the authors conclude that causality cannot be inferred.

Analyses used to determine whether meningiomas or gliomas occurred on the same side of the head as the mobile phone did not find any excess risk for these cancers. While the risk of glioma seemed to be increased for regular users when the phone was used on the same side of the head as the tumour (ispsilateral), biases could account for this result.

No excess risk of these cancers was found for regular users whether they used analogue or digital mobile phones.

The authors conclude that, 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.

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