Introduction

Mobile phone use has increased dramatically in many 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 emitted by mobile phones, and recommended research into the possible adverse health effects of mobile telephone use. 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.

Interphone was therefore initiated as an international set of case–control studies\(^1\) focussing 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 carcinogenic. The methods, results and conclusions are provided here and thus this report to the UICC marks the completion of the Interphone Study.

Methodology

The study was conducted in 13 countries, Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden, and the UK using a common core protocol. Interphone was the largest case–control study to date investigating risks related to mobile phone use and to other potential risk factors for the tumours of interest and included 2,765 glioma, 2,425 meningioma, 1,121 acoustic neuroma, 109 malignant parotid gland tumour cases and 7,658 controls. In addition to a detailed history of mobile phone use, information was collected on a number of known and potential risk factors for the tumours of interest. Particular attention was paid to estimating the amount and direction of potential recall and participation biases\(^2\) and their impact on the study results (see Annex 2).

Source population

\( ^1\) Case-control study: A case–control study involves the identification of individuals with (‘cases’) and without (‘controls’) a particular disease or condition. The prevalence (or level) of exposure to a factor is then measured in each group. If the prevalence of exposure among cases and controls is different, it is possible to infer that the exposure may be associated with an increased or decreased occurrence of the outcome of interest.

\( ^2\) Recall bias: a systematic error due to differences in accuracy or completeness of recall to memory of past events or experiences; participation bias: a systematic error due to a situation of subjects who accept or not to take part differ as to risk.
In Australia, Canada, France, Germany, Italy, Japan and New Zealand, the source population was restricted to major metropolitan areas where mobile phones were first introduced. Major treatment centres for the diseases of interest are concentrated in these areas and most of the population is unlikely to go out of the region for diagnosis and treatment. In all study regions except Paris and Tokyo, it was believed that 90 to 95% of the cases were diagnosed or treated in the collaborating units in the study areas. For practical reasons, limiting the study area to these populations also facilitated face-to-face interviews. In Denmark, Finland, Israel, Norway and Sweden the study was largely nation-wide. The UK-South study was restricted to the South East of England, urban and rural, and the UK-North study encompassed both urban areas and sparsely populated rural areas.

All residents in the study regions aged 30 to 59 were eligible for the study; additional eligibility criteria, such as citizenship and proficiency in the local language were imposed in some study centres. The choice of age-range aimed to maximise the likelihood of exposure. Mobile phone use is a relatively new phenomenon: until the mid-1990’s mobile phone use was mainly restricted to people in the age range most likely to use the phones for business purposes.

**Case eligibility and ascertainment**

Eligible cases were all residents of the study region diagnosed during the study period with a confirmed primary glioma, menigioma, or acoustic neuroma. Eight centres (Australia—Canada—Montreal, Ottawa and Vancouver; Denmark; Israel; Italy; Sweden) also included malignant parotid gland tumours (see Annex 1). Because benign parotid gland tumours may be treated in a very large number of institutions, most centres found it logistically difficult to ensure complete ascertainment, and only Canada—Ottawa, Israel (all histological types) and Sweden included them.

All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. In Australia and Germany, only histologically confirmed tumours were included. In Denmark cases found to have had any previous cancer (excluding non-melanocytic skin cancer) were excluded.

Each centre established procedures for the rapid ascertainment of cases from participating diagnostic and treatment units, which was particularly important for glioma patients, whose health can deteriorate quickly. Every effort was made to maintain a close relationship with the units to ensure that cases were not missed and that the required authorisations were obtained from treating physicians when necessary. Close monitoring of case ascertainment was essential and all study centres, except Finland and Japan, used one or more secondary source (including medical archives, hospital discharge and billing files, and hospital or regional cancer registries) to improve ascertainment levels.

**Control eligibility and selection**

Controls were randomly selected from the source population. The sampling frame depended on the local situation. The study design called for controls to be individually- or frequency-matched to cases, with the number of controls varying according to the tumour type: 1 control per case for brain tumours; 2 for acoustic neuroma; and 3 for parotid gland tumours. In Germany, two controls were selected for each brain tumour case. Controls were matched on year of birth (within 5-year categories), sex and study region.

**Approach to subjects and informed consent**

All cases for whom physician authorisation for contact had been obtained and all controls were initially informed about the study and asked to participate. The procedures varied between centres, depending on the requirements of local Ethics Review Boards. In seven centres, the cases were initially approached by the treating physician or a nurse for consent to be included in the study. In other study centres approaches included: active case ascertainment by the study staff followed by physician authorisation to contact each case directly; blanket approval to contact all eligible cases; or a mix of the two. In all centres participants provided signed informed consent.
Collection of information on individual study subjects
Whenever possible, consenting subjects were interviewed face-to-face by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire. Only Finland used a paper version of the questionnaire. In exceptional cases, telephone interviews were conducted with difficult-to-reach subjects. If subjects became too tired or confused to complete the interview in one session a second appointment was arranged; a partner or other family member could assist in the interview. When the study subject had died or was too ill to participate, a proxy respondent was interviewed where this was possible and permitted by ethics committees. In Australia and New Zealand an abbreviated questionnaire was used for proxy interviews. Controls who refused to participate in the study were asked, whenever possible, to complete a short non-respondent questionnaire in all centres, except in Denmark and UK-South, in order to evaluate whether they differed from participating controls. A small number of cases in some centres also completed the non-respondent questionnaire.

The study questionnaire covered demographic factors, mobile phone use (detailed below), use of other wireless communication devices, occupational exposures to EMF and other potential confounders or risk factors for the diseases of interest (including exposure to ionising radiation, smoking and the subject’s personal and familial medical history). Specific questions on exposure to loud noise and hearing loss were asked of acoustic neuroma cases and their controls.

History of mobile phone use
Detailed questions were asked of regular mobile phone users, defined as those with an average of at least one call per week for a period of 6 months or more, concerning their history of phone use. A paper calendar was handed to the subject. Together, the respondent and interviewer attempted to identify each phone used (aided by show cards with pictures of hundreds of models of mobile phones that were compiled and updated during the course of the study) and to reconstruct the time period during which it was used. This provided the subject with a visual record of the phone history when responding to the subsequent detailed questions.

For each phone, detailed questions were asked about the initial pattern of use, including network operator and average number and duration of calls, and any subsequent changes in use patterns. Questions were also asked about the proportion of time the phones were used in urban, suburban or rural settings, while stationary or moving in a vehicle, how often the antenna was extended, and whether headsets or hands-free kits were used. The side of the head on which the phone was usually held (i.e. the laterality of phone use) and the handedness (left or right-handed) of the subject were recorded.

Validation studies
Validation studies were conducted to assess the accuracy of subjects’ recall of their history of mobile phone use. Short-term recall was assessed in volunteer subjects using either software modified phones or network operators’ records in eleven countries. Validation of medium- to long-term recall of phone use in comparison with network operator records was possible in three countries (Australia, Canada and Italy) for cases and controls, while validation of short-term recall was possible for some subjects in Denmark, Israel, and Sweden.3

Diagnostic information
Detailed diagnostic information was obtained from medical records for all cases interviewed and for non-interviewed cases in most study centres. This information included anatomical location and side of the tumour and histopathology, including whether benign, malignant or of uncertain behaviour.

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3 A more detailed account of validation as conducted in the course of the Interphone study is given in Annex 2.
Localisation of brain tumours
Since intracranial RF energy deposition from mobile phones is non-uniform, with most of the energy absorbed in the vicinity of the phone, the probable location of the origin of the brain tumours was identified so that the RF “exposure” at that location could be evaluated. Neuro-radiologists in each centre reviewed radiological images (Magnetic Resonance Imaging and Computed Tomography scans) or records and recorded tumour location on a generic 3-dimensional grid map of the human head, made up of cubes 1 cm³ in size, which was developed for the purpose.

Data quality assurance
The CAPI questionnaire included many checks: the sequence of questions was constrained with little opportunity to skip questions and automatic range and consistency checks were incorporated. After completion of the interviews, routine checks were performed on the data from all centres both locally and centrally. Inconsistencies and ambiguities were identified and resolved wherever possible.

Assessment of exposure from mobile phones
Indices of exposure, including cumulative call time, average call duration and cumulative number of calls, overall and within specific time-windows, with and without use of hands-free devices, were computed using the detailed information reported by regular users.

Missing data
To avoid exclusion of subjects with missing responses to questions about mobile phone use (which might be more frequent in cases and long-term users and hence lead to a bias), rules were developed for the imputation of missing data. Hierarchical rules were defined a priori, and the same imputation procedure was applied to each pertinent instance. For example, if the number or duration of calls made during a specific time period was missing, but the subject provided information for adjacent time periods, the value was imputed as the average of the two adjacent periods. When this information was not available, the imputed value was the median use of all other users, in the same period and region.

Results

Glioma and meningioma
A reduced odds ratio (OR)⁴ 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 10⁻⁰ decile of recalled cumulative call time, ≥1640h, 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 are 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 and meningioma 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.

Acoustic neuroma
The odds ratio (OR) of acoustic neuroma with ever having been a regular mobile phone user was 0.85 (95% confidence interval 0.69–1.04). The OR for ≥10 years after first regular mobile phone use was 0.76 (0.52–

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⁴ In theory, an odds ratio of one means that both cases and controls had the same odds of exposure and, therefore, the exposure probably is not linked to the risk of cancer. An odds ratio greater than one suggests that the exposure may increase the risk of cancer.
1.11). There was no trend of increasing ORs with increasing cumulative call time or cumulative number of calls, with the lowest OR (0.48 (0.30-0.78)) observed in the 9th decile of cumulative call time. In the 10th decile (≥1640 hours) of cumulative call time, the OR was 1.32 (0.88-1.97); there were, however, implausible values of reported use in those with ≥1640 hours of accumulated mobile phone use. With censoring at 5 years before the reference date the OR for ≥10 years after first regular mobile phone use was 0.83 (0.58-1.19) and for ≥1640 hours of cumulative call time it was 2.79 (1.51-5.16), but again with no trend in the lower nine deciles and with the lowest OR in the 9th decile. In general, ORs were not greater in subjects who reported usual phone use on the same side of the head as their tumour than in those who reported it on the opposite side, but it was greater in those in the 10th decile of cumulative hours of use.

Conclusions

Glioma and meningioma
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.

Acoustic neuroma
There was no increase in risk of acoustic neuroma with ever regular use of a mobile phone or for users who began regular use 10 years or more before the reference date. Elevated odds ratios observed at the highest level of cumulative call time could be due to chance, reporting bias or a causal effect. As acoustic neuroma is usually a slowly growing tumour, the interval between introduction of mobile phones and occurrence of the tumour might have been too short to observe an effect, if there is one.
Parotid gland tumours

The largest of the salivary glands are the parotid glands, located in each cheek over the jaw in front of the ears. As they therefore grow in an area of the head where the mobile phone is held to the ear, it was another outcome included in Interphone. Malignant parotid tumours are rare with less than 1 new patient per year per 100,000 persons. Therefore the ascertainment of parotid gland tumour patients was an optional part of Interphone from the very beginning, with participation of Australia, Canada, Denmark, Israel, Italy, Norway and Sweden; only in Canada-Ottawa, Israel (all histological types including pleomorphic and Warthin's) and Sweden also patients with benign parotid gland tumours were asked to participate. Denmark/Sweden (jointly) and Israel published their national findings already in 2006 and 2008 including 632 cases, taking benign and malignant tumours together. As the other centers would only provide data of 57 additional interviewed patients with a malignant parotid gland tumour, the principal investigators of the respective centers and IARC jointly decided not to further pool these data at this stage but prioritize other research questions within the Interphone consortium.
Validation studies
A major strength of the Interphone study was the conduct of several validation studies to assist in assessing the study’s strengths and limitations and inform the researchers about possible shortcomings when interpreting the main results. In this context Interphone is quite unique among epidemiological studies on health effects of mobile phone use and the insight obtained from the validation studies is also informative when it comes to evaluating other studies in this field.

Information on persons not participating in the study
Non-response questionnaires (NRQ) were completed by a sub-set of nonparticipants among both cases and controls. Over- or under-representation of mobile phone users among those who participated would lead to a bias in the risk analysis, and to know the likely magnitude of this bias is important for the interpretation of results. In fact, regular mobile phone use was reported less frequently by controls and cases completing the NRQ, suggesting that mobile phone users were over-represented among participants. Lower education and more recent start of mobile phone use were also found more frequently among nonparticipants. Altogether these observations could result in a downward bias of around 10% in the risk of regular mobile phone use. This would explain a tendency of observing lower risk estimates in Interphone, but also suggests that in some groups nonparticipation alone would not explain the decrease in risk.

Radiofrequency exposure from mobile phone handsets
Using amount of mobile phone use as exposure variable assumes that the more one uses the mobile phone the more the exposure to radiofrequency electromagnetic fields (RF) cumulates over time; that is that the heaviest users of mobile phones have the greatest risk, if any. The output power of a mobile phone is directly related to RF strength and may theoretically vary substantially in different networks and phone use circumstances due to power control technologies. Hence, heavy mobile phone users with mainly calls under low output power may have lower RF exposure than less frequent mobile phone users with mainly calls under high output power conditions. More than 500 volunteers in 12 countries used software-modified phones for approximately 1 month recording date, time, and duration of each call, and the frequency band and output power at fixed time intervals throughout each call. Measurements of over 60,000 phone calls showed that the average output power was approximately 50% of the maximum and that maximum power was used during a considerable proportion of call time (39% on average). Output power decreased with increasing call duration, but showed little variation in relation to other factors except higher average output power in very sparsely populated areas. Amount of mobile phone use appears to predict RF exposure well, but could be improved by accounting for average power levels of different telecommunications systems. There appears to be little value in gathering information on circumstances of mobile phone use other than use in very sparsely populated regions.

Self-reported use of mobile phones: validation using network operator data
Two validation studies were conducted to investigate how well or not people can recall and report their current and past mobile phone use. For this purpose self-reported mobile phone use was compared to mobile phone use recorded by the network operators. In study #1, mobile phone use of 672 volunteers in 11 countries was recorded by operators or through the use of software-modified phones, and compared to use recalled six months later. On average, interviewees underestimated the number of calls per month, whereas duration of calls was overestimated (called “random error”). The reporting error varied with actual use, showing underestimation in light users and overestimation in heavy users (called “systematic error”). In summary, volunteer subjects recalled their recent phone use with moderate systematic error and substantial random error. While systematic error may lead to overestimation of a risk, if any, random error can be expected to underestimate the risk, if one exists. In study #2, mobile
phone records of 212 cases and 296 controls were collected from network operators in Australia, Canada, and Italy over an average of 2 years, and compared with mobile phone use reported at interview. It confirmed the observations of study #1 in regard to the systematic and random error. For cases, but not controls, overestimation of mobile phone use increased with increasing time before the interview. In conclusion, cases and controls had similar problems with recalling past mobile phone use, however, the suggestion of an overestimation of mobile phone use by cases in more distant time periods could cause a bias towards an overestimation of a risk.

**Conclusions from validation studies**

The comprehensive validation studies are a unique feature of Interphone, enabling the researchers to quantify problems persistent in this type of observational studies and to assist in the interpretation. However, albeit the huge effort, competing biases were identified, with some expected to lead to an underestimation and others leading to an overestimation of the risk. Although the validation studies were informative on the nature, direction and magnitude of most biases, the observed biases were themselves related to uncertainty because they were measured in samples or with some error. Consequently, applying different error scenarios that would all be possible taking the results from the validation studies into account, could not resolve whether the increased risks for glioma and acoustic neuroma observed in the above-mentioned group of heaviest mobile phone users indicates a causal effect or reflects recall or participation problems. This led to the overall conclusion that bias and error prevent a causal interpretation.
List of Publications:

Interphone publications


Validation studies


National and sub-set publications using Interphone data (mobile phones or RF exposure, further methodological aspects)

2011


2010

2009


2008


2007


2006


2005


2004 or earlier


List of Principal Investigators:

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<tr>
<th>Country</th>
<th>Investigator</th>
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<tr>
<td>IARC</td>
<td>Dr Elisabeth Cardis</td>
</tr>
<tr>
<td>Australia</td>
<td>Dr Bruce Armstrong</td>
</tr>
<tr>
<td>Canada-Montreal</td>
<td>Dr Jack Siemiatycki</td>
</tr>
<tr>
<td>Canada-Ottawa</td>
<td>Dr Daniel Krewski</td>
</tr>
<tr>
<td>Canada-Vancouver</td>
<td>Dr Mary McBride</td>
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<tr>
<td>Denmark</td>
<td>Dr Christoffer Johansen</td>
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<td>Finland</td>
<td>Dr Christoffer Johansen</td>
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<tr>
<td>France</td>
<td>Dr Martine Hours</td>
</tr>
<tr>
<td>Germany</td>
<td>Dr Joachim Schüz</td>
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<tr>
<td>Israel</td>
<td>Dr Siegal Sadetzki</td>
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<tr>
<td>Italy</td>
<td>Dr Susanna Lagorio</td>
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<tr>
<td>Japan</td>
<td>Dr Naohito Yamaguchi</td>
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<tr>
<td>New Zealand</td>
<td>Dr Alistair Woodward</td>
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<tr>
<td>Norway</td>
<td>Dr Tore Tynes</td>
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<td>Dr Maria Feychting</td>
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