International study
INTERPHONE

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The **INTERPHONE Study**, a series of multinational case–control studies set-up to determine whether mobile telephone use increases the risk of cancer and, specifically, whether the **radiofrequency radiation** emitted by mobile telephones is carcinogenic, is nearing completion.

Separate studies have being carried out for acoustic neurinoma, glioma, meningioma and tumours of the parotid gland. The studies used a common core protocol and were carried out in Australia, Canada, Denmark, Finland, France, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden and the UK. Details of the study protocol and procedures have been published (Cardis, Richardson et al, 2007 – Springer Open. Access [http://www.springerlink.com/content/x88uu6q103076p53/](http://www.springerlink.com/content/x88uu6q103076p53/)).

The study includes approximately 2600 gliomas, 2300 meningiomas, 1100 acoustic neurinomas, 400 parotid gland tumours and their respective controls. This is by far the largest epidemiological study of these tumours to date (Cardis, Richardson 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 (Christensen et al 2004, 2005; Hepworth et al, 2006; Hours et al, 2007; Klaeboe et al, 2007; Lahkola et al, 2007; Lonn et al, 2004, 2005, 2006; Sadetzkii et al, 2007; Schlehofer et al, 2007; Schoemaker et al, 2006; Schulz et al, 2006; Takebayashi et al, 2006, 2008) and are summarised in Table 1. In most studies, the OR related to ever having been a regular mobile phone user was below 1, in some instances statistically significantly so, possibly reflecting participation bias or other methodological limitations.

For glioma, although results by time since start of use and amount of phone use vary, the number of long-term users is small in individual countries and results are therefore compatible. Pooling of data from Nordic countries and part of the UK yielded a significantly increased risk of glioma related to use of mobile phones for a period of 10 years or more on the side of the head where the tumour developed (Lahkola et al, 2007). This finding could either be causal or artifactual, related to differential recall between cases and controls.

In the Japanese study (Takebayashi et al, 2008), efforts were made to evaluate the maximum amount of RF energy absorbed at the location of the tumour; such analyses, gave an OR of 1.55 (95% CI 0.57, 4.19) related to the highest quartile of cumulative phone time weighted by maxSAR, based on 15 exposed cases; the OR was 5.84 (95% CI 0.96, 35.60) for subjects with cumulative maxSAR-hours of 10 or more W kg⁻¹–hour; this result, based on few subjects (7 cases and 4 controls) needs to be investigated further.

For meningioma and acoustic neurinoma, most national studies provided little evidence of an increased risk. The numbers of long-term and heavy users in individual studies were even smaller than for glioma, however, and prevent any definitive conclusion about a possible association between mobile telephone use and the risk of these tumours. Pooled analyses of data from Nordic countries and the UK found no increased risk of meningioma in relation to long term or heavy use (Lahkola et al, 2008), but a a significantly increased risk of acoustic neurinoma related to durations of use of 10 years or more on the side of tumour (Schoemaker et al, 2006). Again, this finding could either be causal or artifactual, related to differential recall between cases and controls.
For parotid gland tumours, no increased risk was observed overall for any measure of exposure investigated. In a combined analysis of data from Sweden and Denmark (Lonn et al, 2006), a nonsignificantly increased risk of benign tumours was observed for ipsilateral use 10 years or more, while a decreased risk was seen for contralateral use, possibly reflecting differential recall between cases and controls. In the Israeli study, where study subjects tended to report substantially heavier use of mobile phones, results suggest a possible relation between heavy mobile phone use and risk of parotid gland tumours. Additional investigations of this association, with longer latency periods and large numbers of heavy users, are needed to confirm these findings.

A number of methodological papers have been published or are in preparation (Vrijheid, Deltour et al, 2006; Vrijheid, Cardis et al, 2006; Cardis, Richardson et al, 2007; Berg et al, 2005; Hepworth et al, 2006; Parslow et al, 2003; Samkange-Zeeb et al, 2004; Lakhola et al, 2005; Cardis et al, 2008; Vrijheid et al 2008; Tokola et al, 2008; Vrijheid et al, accepted), addressing issues of study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study:

- Validation studies were conducted to evaluate potential error in the recall of phone, indicating that of phone use was subject to moderate systematic and substantial random error (Vrijheid, Cardis et al., 2006, Vrijheid et al 2008). Errors appeared to be larger for duration of calls than for number of calls, and phone use was under-estimated by light users and over-estimated by heavy users. Comparison of a sample of cases and controls in three countries showed little evidence for differential recall errors overall or in recent time periods, but apparent overestimation by cases in more distant time periods (Vrijheid et al 2008).

- The possible effects of recall errors were evaluated using Monte-Carlo computer simulations. Results suggest that random recall errors can lead to a large underestimation in the risk of brain cancer associated with mobile phone use. The large random errors seen in the validation study were found to have larger impact than plausible systematic errors. Differential errors in recall had very little additional impact in the presence of large random errors (Vrijheid et al, 2006). However, the apparent overestimation by cases in more distant time periods could cause positive bias in estimates of disease risk associated with mobile phone use (Vrijheid et al, 2008).

- Potential for selection bias was also evaluated, using information from non-response questionnaires completed by a sub-set of non-participants. This study suggests that refusal to participate is related to less prevalent use of mobile phones, and that this could result in a downward bias in odds ratios for regular mobile phone use (Vrijheid et al, accepted).

- Because exposure to RF from phones is localized, if a risk exists it is likely to be greatest for tumours in regions with greatest energy absorption. The spatial distribution of RF energy in the brain was characterised, using results of measurements made on over 100 phones used in different countries. Most (97–99% depending on frequency) appears to be absorbed in the brain hemisphere on the side where the phone is used, mainly in the temporal lobe. The average relative SAR is highest in the temporal lobe and the cerebellum and decreases very rapidly with increasing depth, particularly at higher frequencies. Analyses of risk by location of tumour are therefore essential for the interpretation of results studies of brain tumours in relation to mobile phone use (Cardis et al, 2008).

Manuscripts presenting results of the international analyses, based on larger numbers of long-term and heavy users and taking into account the results of these methodological sub-studies are in preparation. More detailed analyses are also underway, focusing on more precise localization of tumors using 3-dimensional radiological images, and on the analysis of the effect of RF exposure at the location of the tumor, using a gradient of RF emitted by mobile phones.
Results of national analyses of the relation between other risk factors and the tumours of interest have also been published or are in press (Berg et al, 2006; Bethke et al, in press; Blettner et al, 2006; Edwards et al, 2006; Malmer et al, 2007; Sadetzki et al, in press; Schlehofer et al, 2007; Schoemaker et al, 2006, 2007a, 2007b; Schuz et al, 2006; Schwartzbaum et al, 2005, 2007; Wigertz et al, 2006, 2007, 2008). These include smoking, allergies, environmental and occupational risk factors, medical radiation, reproductive factors and genes.

Work is underway to further exploit the information on occupational exposures collected within INTERPHONE study with the aims of: 1) evaluating the possible association between occupational exposure to EMF (both ELF and RF/MW) and glioma and meningioma; 2) evaluating the possible association between selected occupational chemical exposures and these tumours and 3) investigating the possibility of synergism and/or confounding between chemical and EMF exposures on the risk of brain cancers. This work involves assessing occupational exposure to EMF and selected chemicals using validated job-exposure matrices, which will be developed within the project and refining this assessment by consolidating information obtained from the JEM with data on exposure variations related to the specific industry in which a subject worked, to the tasks he or she performed and to the actual sources of exposure, available from the INTERPHONE questionnaire.

### Table 1 – Summary of published results from national INTERPHONE analyses of mobile phone use

<table>
<thead>
<tr>
<th>Country</th>
<th>Age range</th>
<th>Diagnosis years</th>
<th>Number of cases and controls</th>
<th>CR and 95% CI Ever regular use # cases</th>
<th>OR and 95% CI Start of use 10 years or more in the past # cases</th>
<th>CR and 95% CI (polar use, start of use 10+ years in past) # cases</th>
<th>OR and 95% CI Contralateral use, start of use 10+ years in past # cases</th>
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<tbody>
<tr>
<td><strong>Glioma</strong></td>
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<tr>
<td>Danmark (Christensen et al, 2005)</td>
<td>20-69</td>
<td>2000-2002</td>
<td>Low-grade 81, High-grade 171</td>
<td>1.08 (0.58, 2.00) 47 0.37 (0.09, 0.90) 59</td>
<td>1.64 (0.44, 5.12) 6 0.19 (0.01, 1.16) 8</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>France (Hours et al, 2007)</td>
<td>30-59</td>
<td>2001-2003</td>
<td>96 1.15 (0.65, 2.05) 59</td>
<td>46 months+ 1.96 (0.74, 5.20) 21</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Germany (Schulze et al, 2006)</td>
<td>30-69</td>
<td>2000-2003</td>
<td>366 0.98 (0.74, 1.29) 138</td>
<td>2.20 (0.94, 5.11) 12</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Japan (Takebayashi et al, 2008)</td>
<td>30-69</td>
<td>2000-2004</td>
<td>83 1.22 (0.63, 2.37) 56</td>
<td>6.5 years + 0.65 (0.20, 1.87) 7</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Norway (Klausboe et al, 2007)</td>
<td>19-69</td>
<td>2001-2002</td>
<td>289 0.8 (0.5, 1.2) 76 0.5 (0.3, 0.9) 161</td>
<td>0.8 (0.5, 1.2) 70</td>
<td>6+ years 1.3 (0.8, 2.1) 39</td>
<td>0.8 (0.5, 1.4) 32</td>
<td>6+ years 0.8 (0.5, 1.5) 11</td>
</tr>
<tr>
<td>Sweden (Lonn et al, 2005)</td>
<td>20-69</td>
<td>2000-2002</td>
<td>371 0.6 (0.4, 1.0) 214 0.5 (0.3, 0.9) 161</td>
<td>0.9 (0.5, 1.5) 25</td>
<td>1.6 (0.8, 3.4) 15</td>
<td>1.5 (0.7, 3.1) 11</td>
<td>0.7 (0.3, 1.5) 11</td>
</tr>
<tr>
<td>UK (Hewishworth et al, 2006)</td>
<td>18-69</td>
<td>2000-2004</td>
<td>966 0.78 (0.71, 1.3) 58 0.78 (0.71, 1.3) 58</td>
<td>0.95 (0.74, 1.23) 143</td>
<td>0.78 (0.71, 1.37) 77</td>
<td>0.98 (0.71, 1.37) 67</td>
<td>0.98 (0.71, 1.37) 67</td>
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<tr>
<td><strong>Meningioma</strong></td>
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<tr>
<td>Danmark (Christensen et al, 2005)</td>
<td>20-69</td>
<td>2000-2002</td>
<td>175 0.83 (0.54, 1.28) 67</td>
<td>1.02 (0.32, 3.24) 6</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>France (Hours et al, 2007)</td>
<td>30-59</td>
<td>2001-2003</td>
<td>145 0.74 (0.43, 1.28) 71 46 months+ 0.73 (0.28, 1.91) 45</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Germany (Schulze et al, 2006)</td>
<td>30-69</td>
<td>2000-2003</td>
<td>381 0.84 (0.62, 1.13) 104</td>
<td>1.09 (0.35, 3.37) 5</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Japan (Takebayashi et al, 2008)</td>
<td>30-69</td>
<td>2000-2004</td>
<td>128 0.70 (0.42, 1.16) 55 5.2 years 1.59 (0.52, 2.11) 30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Norway (Klausboe et al, 2007)</td>
<td>19-69</td>
<td>2001-2002</td>
<td>207 0.8 (0.5, 1.1) 98 0.6 (0.4, 1.0) 214</td>
<td>1.0 (0.6, 1.8) 36</td>
<td>6+ years 1.1 (0.6, 2.3) 17</td>
<td>1.2 (0.6, 2.3) 18</td>
<td>5.2 years 1.05 (0.52, 2.11) 30</td>
</tr>
<tr>
<td>Sweden (Lonn et al, 2005)</td>
<td>20-69</td>
<td>2000-2002</td>
<td>272 0.7 (0.5, 0.9) 118 0.9 (0.4, 1.9) 8 1.3 (0.5, 3.9) 5</td>
<td>0.5 (0.1, 1.7) 3</td>
<td>NA</td>
<td>NA</td>
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<td>Nordic combined (Lahkiola et al, 2008)</td>
<td>2000-2004</td>
<td>1,093 0.76 (0.65, 0.89) 573</td>
<td>0.91 (0.67, 1.25) 73</td>
<td>1.05 (0.67, 1.65) 33</td>
<td>0.62 (0.38, 1.03) 24</td>
<td>0.62 (0.38, 1.03) 24</td>
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<tr>
<td><strong>Acoustic neurinoma</strong></td>
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<tr>
<td>Danmark (Christensen et al, 2004)</td>
<td>20-69</td>
<td>2000-2002</td>
<td>106 0.90 (0.51, 1.57) 45 0.22 (0.04, 1.11) 2</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>France (Hours et al, 2007)</td>
<td>30-59</td>
<td>2001-2003</td>
<td>109 0.92 (0.53, 1.59) 58 46 months+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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</tr>
</tbody>
</table>


