INTERPHONE Study

Results update – 7 February 2008

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 **radio-frequency 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/).

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. A number of methodological papers have been submitted or published (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), addressing issues of study design, participation bias, recall error and exposure assessment that are essential in the interpretation of results from the study.

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; Sadetzki et al, 2007; Schlehofer et al, 2007; Schoemaker et al, 2006; Schuz 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. A pooled analysis of data from Nordic countries and the UK found 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 non-significantly 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.

Manuscripts presenting results of the international analyses, based on much larger numbers of long-term and heavy users 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. Adjustment for exposure measurement error based on data from the validation studies is also being conducted in order to assess the impact of these errors on risk.

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). These include smoking, allergies, environmental and occupational risk factors, medical radiation and genes.

Work is starting 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

Country	Age range	Diagnosis years	Number of cases and controls	OR and 95% CI Ever regular use	# cases	OR and 95% CI Start of use 10 years or more in the past	# cases	OR and 95% CI Ipsilateral use, start of use 10+ years in past	# cases	OR and 95% CI Contralateral use, start of use 10+ years in past	# cases
Glioma											
Denmark (Christensen et al, 2005)	20-69	2000-2002	Low-grade 81 155 High-grade 171 330	Low-grade 1.08 (0.58, 2.00) High-grade 0.58 (0.37, 0.90)	47 59	Low-grade 1.64 (0.44, 6.12) High-grade 0.48 (0.19, 1.26)	6 8	NA		NA	
France (Hours et al, 2007)	30-59	2001-2003	96 96	1.15 (0.65, 2.05)	59	*46 months+ 1.96 (0.74, 5.20)*	*21*	NA		NA	
Germany (Schuz et al, 2006)	30-69	2000-2003	366 1,494	0.98 (0.74, 1.29)	138	2.20 (0.94, 5.11)	12	NA		NA	
Japan (Takebayashi et al, 2008)	30-69	2000-2004	83 163	1.22 (0.63, 2.37)	56	*6.5 years + 0.60 (0.20, 1.78)*	*7*	NA		NA	
Norway (Klaeboe et al 2007)	19-69	2001-2002	289 358	0.6 (0.4, 0.9)	161	*6+ years 0.8 (0.5, 1.2)*	70	*6+ years 1.3 (0.8, 2.1)*	*39*	*6+ years 0.8 (0.5, 1.4)*	*32*
Sweden (Lonn et al, 2005)	20-69	2000-2002	371 674	0.8 (0.6, 1.0)	214	0.9 (0.5, 1.5)	25	1.6 (0.8, 3.4)	15	0.7 (0.3, 1.5)	11
UK (Hepworth et al, 2006)	18-69	2000-2004	966 1,716	0.94 (0.78,1.13)	508	0.90 (0.63,1.28)	66	NA		NA	
Nordic combined (Lahkola et al, 2007)		2000-2004	1,522 3,301	0.78 (0.68, 0.91)	867	0.95 (0.74, 1.23)	143	1.39 (1.01, 1.92)	77	0.98 (0.71, 1.37)	67
Meningioma											
Denmark (Christensen et al, 2005)	20-69	2000-2002	175 316	0.83 (0.54, 1.28)	67	1.02 (0.32, 3.24)	6	NA		NA	
France (Hours et al, 2007)	30-59	2001-2003	145 145	0.74 (0.43, 1.28)	71	46 months+ *0.73 (0.28, 1.91)*	*15*	NA		NA	
Germany (Schuz et al, 2006)	30-69	2000-2003	381 762	0.84 (0.62, 1.13)	104	1.09 (0.35, 3.37)	5	NA		NA	
Japan (Takebayashi et al, 2008)	30-69	2000-2004	128 229	0.70 (0.42, 1.16)	55	*5.2 years + 1.05 (0.52, 2.11)*	*30*	NA		NA	
Norway (Klaeboe et al 2007)	19-69	2001-2002	207 358	0.8 (0.5, 1.1)	98	*6+ years 1.0 (0.6, 1.8)*	*36*	*6+ years 1.1 (0.6, 2.3)*	*17*	*6+ years 1.2 (0.6, 2.3)*	*18*
Sweden (Lonn et al, 2005)	20-69	2000-2002	273 674	0.7 (0.5, 0.9)	118	0.9 (0.4, 1.9)	8	1.3 (0.5, 3.9)	5	0.5 (0.1, 1.7)	3
Acoustic neurinoma											
Denmark (Christensen et al, 2004)	20-69	2000-2002	106 212	0.90 (0.51, 1.57)	45	0.22 (0.04, 1.11)	2	NA		NA	
France (Hours et al, 2007)	30-59	2001-2003	109 214	0.92 (0.53, 1.59)	58	*46 months+ 0.66 (0.28, 1.57)*	*14*	NA		NA	
Germany	30-69	2000-2003	97 194	0.67 (0.38, 1.19)	29	NA	0	NA		NA	

Country	Age range	Diagnosis years	Number of cases and controls	OR and 95% CI Ever regular use # cases	OR and 95% CI Start of use 10 years or more in the past # cases	OR and 95% CI Ipsilateral use, start of use 10+ years in past # cases	OR and 95% CI Contralateral use, start of use 10+ years in past # cases
(Schlehofer et al, 2007)							
Japan (Takebayashi et al, 2006)	30-69	2000-2004	101 339	0.73 (0.43, 1.23) 51	*8+ years* *0.79 (0.24, 2.65) 4*	NA	NA
Norway (Klaeboe et al 2007)	19-69	2001-2002	45 358	0.5 (0.2, 1.0) 22	*6+ years* *0.5 (0.2, 1.4) 8*	*6+ years* *0.9 (0.3, 2.8) 5*	*6+ years* *0.8 (0.2, 2.5) 4*
Sweden (Lonn et al, 2004)	20-69	1999-2002	148 604	1.0 (0.6, 1.5) 89	1.9 (0.9, 4.1) 14	3.9 (1.6, 9.5) 12	0.8 (0.2, 2.9) 4
Nordic combined (Schoemaker et al, 2005)		1999-2004	678 3,553	0.9 (0.7, 1.1) 360	1.0 (0.7, 1.5) 47	1.3 (0.8, 2.0) 31 *1.8 (1.1-3.1)* 23*	1.0 (0.6, 1.7) 20 *0.9 (0.5, 1.8)* 12*
Parotid gland tumours							
Israel (Sadetzki et al, 2007)	18+	2001-2003	Total 460 1,266 Benign 402 1,072 Malignant 58 294	Total 0.87 (0.68, 1.13) 285 Benign 0.85 (0.64, 1.12) 252 Malignant 1.06 (0.54, 2.10) 33	Total 0.86 (0.42, 1.77) 13 *Total – regular users only* *1.45 (0.82, 2.57) 13*	Total 1.60 (0.68, 3.72) 10 Benign 1.97 (0.81, 4.85) 10	Total 0.58 (0.15, 2.32) 3
Sweden and Denmark (Lonn et al, 2006)	20-69	2000-2002	Benign 112 321 Malignant 60 681	Benign 0.9 (0.5, 1.5) 77 Malignant 0.7 (0.4, 1.3) 25	Benign 1.4 (0.5, 3.9) 7 Malignant 0.4 (0.1, 2.6) 2	Benign 2.6 (0.9, 7.9) 6 Malignant 0.7 (0.1, 5.7) 1	Benign 0.3 (0.0, 2.3) 1 Malignant NA 0

* Analysis by duration of use instead of time since start of use.

Publications

Berg G, Schuz J, Samkange-Zeeb F, Blettner M. Assessment of radiofrequency exposure from cellular telephone daily use in an epidemiological study: German Validation study of the international case-control study of cancers of the brain--INTERPHONE-Study. J Expo Anal Environ Epidemiol. 2005 May;15(3):217-24.

Berg G, Spallek J, Schuz J, Schlehofer B, Bohler E, Schlaefer K, Hettinger I, Kunna-Grass K, Wahrendorf J, Blettner M; Interphone Study Group, Germany. Occupational exposure to radio frequency/microwave radiation and the risk of brain tumors: Interphone Study Group, Germany. Am J Epidemiol. 2006 Sep 15;164(6):538-48. Epub 2006 Jul 27.

Bethke, L., Webb, E, Murray, A, Schoemaker, M., Johansen, C., Christensen, H., Muir, K., McKinney, P., Hepworth, S., Dimitropoulou, P., Feychting, M., Malmer, B., Auvinen, A., Swerdlow, A., Houlston, R. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. Human Molecular Genetics (in press)

Blettner M, Schlehofer B, Samkange-Zeeb F, Berg G, Schlaefer K, Schuz J. Medical exposure to ionising radiation and the risk of brain tumours: Interphone study group, Germany. Eur J Cancer. 2007 Sep;43(13):1990-8. Epub 2007 Aug 8.

Cardis E, Richardson L, Deltour I, Armstrong B, Feychting M, Johansen C, Kilkenny M, McKinney P, Modan B, Sadetzki S, Schuz J, Swerdlow A, Vrijheid M, Auvinen A, Berg G, Blettner M, Bowman J, Brown J, Chetrit A, Christensen HC, Cook A, Hepworth S, Giles G, Hours M, Iavarone I, Jarus-Hakak A, Klaeboe L, Krewski D, Lagorio S, Lonn S, Mann S, McBride M, Muir K, Nadon L, Parent ME, Pearce N, Salminen T, Schoemaker M, Schlehofer B, Siemiatycki J, Taki M, Takebayashi T, Tynes T, van Tongeren M, Vecchia P, Wiart J, Woodward A, Yamaguchi N. The INTERPHONE study: design, epidemiological methods, and description of the study population. Eur J Epidemiol. 2007 Jul 18; [Epub ahead of print – OPEN ACESS] http://www.springerlink.com/content/x88uu6q103076p53/

Christensen HC, Schuz J, Kosteljanetz M, Poulsen HS, Boice JD Jr, McLaughlin JK, Johansen C. Cellular telephones and risk for brain tumors: a population-based, incident case-control study. Neurology. 2005 Apr 12;64(7):1189-95. Erratum in: Neurology. 2005 Oct 25;65(8):1324.

Christensen HC, Schuz J, Kosteljanetz M, Poulsen HS, Thomsen J, Johansen C. Cellular telephone use and risk of acoustic neuroma. Am J Epidemiol. 2004 Feb 1;159(3):277-83.

Edwards CG, Schwartzbaum JA, Lonn S, Ahlbom A, Feychting M. Exposure to loud noise and risk of acoustic neuroma. Am J Epidemiol. 2006 Feb 15;163(4):327-33. Epub 2005 Dec 15. Erratum in: Am J Epidemiol. 2006 Jun 15;163(12):1163.

Hepworth SJ, Bolton A, Parslow RC, van Tongeren M, Muir KR, McKinney PA. Assigning exposure to pesticides and solvents from self-reports collected by a computer assisted personal interview and expert assessment of job codes: the UK Adult Brain Tumour Study. Occup Environ Med. 2006 Apr;63(4):267-72.

Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren MJ, McKinney PA. Mobile phone use and risk of glioma in adults: case-control study. BMJ. 2006 Apr 15;332(7546):883-7. Epub 2006 Jan 20.

Hours M, Bernard M, Montestrucq L, Arslan M, Bergeret A, Deltour I, Cardis E. [Cell Phones and Risk of brain and acoustic nerve tumours: the French INTERPHONE case-control study.] Rev Epidemiol Sante Publique. 2007 Sep 10; [Epub ahead of print] French.

Hours M, Montestrucq L, Arslan M, Bernard M, El Hadjimoussa H, Vrijheid M, Deltour I, Cardis E. (2007) Validation des outils utilisés pour la mesure de la consommation téléphonique mobile dans l'étude INTERPHONE en France. Environnement, risques et Santé. Volume 6 (2), 101-9.

Klaeboe L, Blaasaas KG, Tynes T. Use of mobile phones in Norway and risk of intracranial tumours. Eur J Cancer Prev. 2007 Apr;16(2):158-64

Lahkola A, Auvinen A, Raitanen J, Schoemaker MJ, Christensen HC, Feychting M, Johansen C, Klaeboe L, Lonn S, Swerdlow AJ, Tynes T, Salminen T. Mobile phone use and risk of glioma in 5 North European countries. Int J Cancer. 2007 Apr 15;120(8):1769-75.

Lahkola A, Salminen T, Auvinen A. Selection bias due to differential participation in a case-control study of mobile phone use and brain tumors. Ann Epidemiol. 2005 May;15(5):321-5.

Lönn S, Ahlbom A, Hall P, Feychting M. Mobile phone use and the risk of acoustic neuroma. Epidemiology 2004;15:653-659.

Lönn S, Ahlbom A, Hall P, Feychting M; Swedish Interphone Study Group. Long-term mobile phone use and brain tumor risk. Am J Epidemiol. 2005 Mar 15;161(6):526-35.

Malmer BS, Feychting M, Lonn S, Lindstrom S, Gronberg H, Ahlbom A, Schwartzbaum J, Auvinen A, Collatz-Christensen H, Johansen C, Kiuru A, Mudie N, Salminen T, Schoemaker MJ, Swerdlow AJ, Henriksson R. Genetic variation in p53 and ATM haplotypes and risk of glioma and meningioma. J Neurooncol. 2007 May;82(3):229-37. Epub 2006 Dec 7.

Parslow RC, Hepworth SJ, McKinney PA. Recall of past use of mobile phone handsets. Radiat Prot Dosimetry. 2003;106(3):233-40.

Sadetzki S, Chetrit A, Jarus-Hakak A, Cardis E, Deutch Y, Duvdevani S, Zultan A, Novikov I, Freedman L, Wolf M Cellphone use and risk of benign and malignant parotid gland tumors - a nationwide case-control study. Am J Epid. Epub 2007 Dec 6. DOI: 10.1093/aje/kwm325

Sadetzki S, Oberman B, Mandelzweig L, Chetrit A, Ben-Tal T, Jarus-Hakak A, Duvdevani S, Cardis E, Wolf M. Smoking and risk of parotid gland tumors- A nationwide case-control study. Cancer (in press).

Samkange-Zeeb F, Berg G, Blettner M. Validation of self-reported cellular phone use. J Expo Anal Environ Epidemiol. 2004 May;14(3):245-8.

Schlehofer B, Schlaefer K, Blettner M, Berg G, Bohler E, Hettinger I, Kunna-Grass K, Wahrendorf J, Schuz J. Environmental risk factors for sporadic acoustic neuroma (Interphone Study Group, Germany). Eur J Cancer. 2007 Jul;43(11):1741-7. Epub 2007 Jun 27.

Schoemaker MJ, Swerdlow AJ, Ahlbom A, Auvinen A, Blaasaas KG, Cardis E, Christensen HC, Feychting M, Hepworth SJ, Johansen C, Klaeboe L, Lonn S, McKinney PA, Muir K, Raitanen J, Salminen T, Thomsen J, Tynes T. Mobile phone use and risk of acoustic neuroma: results of the Interphone case-control study in five North European countries. Br J Cancer. 2005 Oct 3;93(7):842-8.

Schoemaker MJ, Swerdlow AJ, Auvinen A, Christensen HC, Feychting M, Johansen C, Klaeboe L, Lonn S, Salminen T, Tynes T. Medical history, cigarette smoking and risk of acoustic neuroma: an international case-control study. Int J Cancer. 2007a Jan 1;120(1):103-10.

Schoemaker MJ, Swerdlow AJ, Hepworth SJ, McKinney PA, van Tongeren M, Muir KR. History of allergies and risk of glioma in adults. Int J Cancer. 2006 Nov 1;119(9):2165-72.

Schoemaker MJ, Swerdlow AJ, Hepworth SJ, van Tongeren M, Muir KR, McKinney PA. History of allergic disease and risk of meningioma. Am J Epidemiol. 2007b Mar 1;165(5):477-85. Epub 2006 Dec 20.

Schuz J, Bohler E, Berg G, Schlehofer B, Hettinger I, Schlaefer K, Wahrendorf J, Kunna-Grass K, Blettner M. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany).Am J Epidemiol. 2006 Mar 15;163(6):512-20. Epub 2006 Jan 27.

Schuz J, Bohler E, Schlehofer B, Berg G, Schlaefer K, Hettinger I, Kunna-Grass K, Wahrendorf J, Blettner M. Radiofrequency electromagnetic fields emitted from base stations of DECT cordless phones and the risk of glioma and meningioma (Interphone Study Group, Germany). Radiat Res. 2006 Jul;166(1 Pt 1):116-9.

Schwartzbaum J, Ahlbom A, Malmer B, Lonn S, Brookes AJ, Doss H, Debinski W, Henriksson R, Feychting M. Polymorphisms associated with asthma are inversely related to glioblastoma multiforme. Cancer Res. 2005 Jul 15;65(14):6459-65.

Schwartzbaum JA, Ahlbom A, Lonn S, Warholm M, Rannug A, Auvinen A, Christensen HC, Henriksson R, Johansen C, Lindholm C, Malmer B, Salminen T, Schoemaker MJ, Swerdlow AJ, Feychting M. An international case-control study of glutathione transferase and functionally related polymorphisms and risk of primary adult brain tumors. Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(3):559-65.

Takebayashi T, Akiba S, Kikuchi Y, Taki M, Wake K, Watanabe S, Yamaguchi N. Mobile phone use and acoustic neuroma risk in Japan. Occup Environ Med. 2006 Dec;63(12):802-7. Epub 2006 Aug 15.

Takebayashi T, Varsier N, Kikuchi Y, Wake K, Taki M, Watanabe S, Akiba S and Yamaguchi N. Mobile phone use, exposure to radiofrequency electromagnetic field, and brain tumour: a case-control study. Br J Cancer. 2008 Feb; 98: 652-659.

Vrijheid M, Cardis E, Armstrong BK, Auvinen A, Berg G, Blaasaas KG, Brown J, Carroll M, Chetrit A, Christensen HC, Deltour I, Feychting M, Giles GG, Hepworth SJ, Hours M, Iavarone I, Johansen C, Klæboe L, Kurttio P, Lagorio S, Lönn S, McKinney PA, Montestrucq M, Parslow RC, Richardson L, Sadetzki S, Salminen T, Schüz J, Tynes T, Woodward A (2006). Validation of short-term recall of mobile phone use for the Interphone Study. Occupational and Environmental Medicine;63(4) :237-43.

Vrijheid M, Deltour I, Krewski D, Sanchez M, Cardis E (2006). The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J Expo Sci Environ Epidemiol. Jul;16(4):371-84.

Wigertz A, Lonn S, Mathiesen T, Ahlbom A, Hall P, Feychting M; Swedish Interphone Study Group. Risk of brain tumors associated with exposure to exogenous female sex hormones. Am J Epidemiol. 2006 Oct 1;164(7):629-36. Epub 2006 Jul 11.

Wigertz A, Lonn S, Schwartzbaum J, Hall P, Auvinen A, Christensen HC, Johansen C, Klaeboe L, Salminen T, Schoemaker MJ, Swerdlow AJ, Tynes T, Feychting M. Allergic Conditions and Brain Tumor Risk. Am J Epidemiol. 2007 Jul 23; [Epub ahead of print]