FILED ELECTRONICALLY ON October 15, 2013

SUPPLEMENTAL PRE-FILED TESTIMONY
OF LENNART HARDELL, MD, PhD
MPUC Docket No. 2011-00262

Q. On February 1, 2013, you submitted written testimony in this case about the risks of adverse health effects from exposure to low intensity levels of radio frequency ("RF") radiation. Have there been recent developments in the science, or has other relevant information been made available, since your testimony that you wish to bring to the attention of the Maine Public Utility Commission?

A. Yes.

I co-authored *Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones*, published in International Journal of Oncology, 2013. *See* attached Exhibit A and *http://www.spandidos-publications.com/10.3892/ijo.2013.2025*. We present pooled results from two study periods (1997-2003 and 2007-2009) based on 316 participating cases and 3,530 controls. This study confirmed previous results of an association between use of mobile and cordless phones and acoustic neuroma. The risk increased with time since first use. For both mobile and cordless phones the risk was highest in the longest latency group. Tumour volume increased per 100 h of cumulative use and years of latency for wireless phones. Using the meningioma cases as reference entity gave similar results as with population based controls indicating that the results could not be explained by recall or observational bias.

I co-authored *Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use,* published in the International Journal of Oncology. *See* Exhibit B and http://www.spandidos-

publications.com/10.3892/ijo.2013.2111. The purpose of this study was to further explore the relationship between especially long-term (>10 years) use of wireless phones and the development of malignant brain tumours. We conducted a new case-control study of brain tumour cases of both genders aged 18-75 years and diagnosed during 2007-2009. Use of wireless phones, both mobile and cordless, was assessed by a self-administered questionnaire supplemented over the phone. The whole procedure was blind to case or control status. Overall, we found a statistically significant increased risk for malignant brain tumours associated with use of wireless phones, odds ratio (OR)=1.7, 95% confidence interval (CI)=1.04-2.8. The OR for mobile phone use of the analogue type was 1.8, 95% CI=1.04–3.3, increasing with >25 years of latency (time since first exposure) to an OR=3.3, 95% CI=1.6-6.9. Digital 2G mobile phone use rendered an OR=1.6, 95% CI=0.996-2.7, increasing with latency >15-20 years to an OR=2.1, 95% CI=1.2-3.6. The results for cordless phone use were OR=1.7, 95% CI=1.1-2.9, and, for latency of 15-20 years, the OR=2.1, 95% CI=1.2-3.8. Few participants had used a cordless phone for >20-25 years. Digital type of wireless phones (2G and 3G mobile phones, cordless phones) gave increased risk with latency >1-5 years, then a lower risk in the following latency groups, but again increasing risk with latency >15-20 years. Ipsilateral use resulted in a higher risk than contralateral mobile and cordless phone use. Higher ORs were calculated for tumours in the temporal and overlapping lobes. This study confirmed previous results of an association between use of mobile and cordless phones and malignant brain tumours.

I co-authored *Meningioma patients diagnosed 2007--2009 and the association with use of mobile and cordless phones: a case--control study*, published in Environmental Health 2013. *See* attached Exhibit C and http://www.ehjournal.net/content/12/1/60. We performed a case–control study on brain tumour cases of both genders aged 18–75 years and diagnosed during

2007–2009. No conclusive evidence of an association between use of mobile and cordless phones and meningioma was found. An indication of increased risk for meningioma was seen in the group with highest cumulative use but was not supported by statistically significant increasing risk with latency. However, considering the long latency periods that have been reported for the increased meningioma risk associated with exposure to ionizing radiation it is still too early to make a definitive risk assessment. Results for even longer latency periods of wireless phone use than in this study are desirable.

The present results strengthen our previous findings of an increased risk for glioma and acoustic neuroma, since a systematic bias in those studies would have been expected also in this study of meningioma using the same methodology.

I co-authored *Hardell L, Carlberg M. Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones.* Rev Env Health 2013. DOI: 10.1515/reveh-2013-0006. *See* attached Exhibit D. All nine issues on causation according to Hill were evaluated to assess the causal association between long-term wireless phone use and brain tumours, specifically acoustic neuroma and glioma. Epidemiological studies of long-term use and laboratory studies and data on the incidence of brain tumors were considered. We concluded that based on the Hill criteria glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones, which should be regarded as carcinogenic to humans.

I co-authored a June 4, 2013 letter to the Federal Communication Commission summarizing some of the scientific evidence showing that the current FCC exposure limits are inadequate to protect human health and urging the FCC to consider this evidence in its reassessment of the exposure limits. See attached Exhibit E. I also make reference to a

September 3, 2013, letter to the FCC from the American Association for Justice (formerly American Trial Lawyers Association) citing "the growing evidence of harm arising from human exposure to radiofrequency emissions," and urging the FCC to lower its current exposure limits. *See* attached Exhibit F.

An interesting paper was recently authored by DeVocht *et al*, *Environmental risk factors for cancers of the brain,* Occup Environ Med 2013. See attached Exhibit G. I was not aware of this paper (published on January 23, 2013), when I submitted my written testimony on February 1, 2013. The paper explores how existing open-access online databases can be used to consider potential risk factors for rare diseases at an ecological level. Data were obtained from the open, online GLOBOCAN 2008 resource, for incidence rates of brain and nervous system cancers in all available countries of the world. The reviewers cautioned that "ecological studies should not be used to infer causality in a policy context," but also concluded that "the study confirms that mobile phone use may be a risk factor for brain cancer, thereby confirming previous ecological findings." The reviewers also concluded that the "latency between relevant exposure (mobile phone use) and clinical manifestation of the disease (brain and nervous system malignancies) is (at population level) at the very least 11–12 years but should ideally be more than 20 years, which is not reflected in most study designs."

Q. Do the studies and papers you reference alter any opinions or conclusions expressed in your February 1, 2013 testimony?

They offer further support for my opinion that a causal association between low-level RF radiation and adverse health effects can be inferred from the science and that exposure to low-level RF radiation, including at levels and frequencies transmitted by smart meters, poses risks to human health.

 EXHIBIT A

Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones

LENNART HARDELL[1], MICHAEL CARLBERG[1], FREDRIK SÖDERQVIST[1,3] and KJELL HANSSON MILD[2]

[1]Department of Oncology, University Hospital, SE-701 85 Örebro;
[2]Department of Radiation Physics, Umeå University, SE-90187 Umeå, Sweden

Received May 22, 2013; Accepted July 1, 2013

DOI: 10.3892/ijo.2013.2025

Abstract. We previously conducted a case-control study of acoustic neuroma. Subjects of both genders aged 20-80 years, diagnosed during 1997-2003 in parts of Sweden, were included, and the results were published. We have since made a further study for the time period 2007-2009 including both men and women aged 18-75 years selected from throughout the country. These new results for acoustic neuroma have not been published to date. Similar methods were used for both study periods. In each, one population-based control, matched on gender and age (within five years), was identified from the Swedish Population Registry. Exposures were assessed by a self-administered questionnaire supplemented by a phone interview. Since the number of acoustic neuroma cases in the new study was low we now present pooled results from both study periods based on 316 participating cases and 3,530 controls. Unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index (SEI). Use of mobile phones of the analogue type gave odds ratio (OR) = 2.9, 95% confidence interval (CI) = 2.0-4.3, increasing with >20 years latency (time since first exposure) to OR = 7.7, 95% CI = 2.8-21. Digital 2G mobile phone use gave OR = 1.5, 95% CI = 1.1-2.1, increasing with latency >15 years to an OR = 1.8, 95% CI = 0.8-4.2. The results for cordless phone use were OR = 1.5, 95% CI = 1.1-2.1, and, for latency of >20 years, OR = 6.5, 95% CI = 1.7-26. Digital type wireless phones (2G and 3G mobile phones and cordless phones) gave OR = 1.5, 95% CI = 1.1-2.0 increasing to OR = 8.1, 95% CI = 2.0-32 with latency >20 years. For total wireless phone use, the highest risk was calculated for the longest latency time >20 years: OR = 4.4, 95% CI = 2.2-9.0. Several of the calculations in the long latency category were based on low numbers of exposed cases. Ipsilateral use resulted in a higher risk than contralateral for both mobile and cordless phones. OR increased per 100 h cumulative use and per year of latency for mobile phones and cordless phones, though the increase was not statistically significant for cordless phones. The percentage tumour volume increased per year of latency and per 100 h of cumulative use, statistically significant for analogue phones. This study confirmed previous results demonstrating an association between mobile and cordless phone use and acoustic neuroma.

Correspondence to: Dr Lennart Hardell, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden
E-mail: lennart.hardell@orebroll.se

Present address: [3]Department of Public Health and Community Medicine, County Council of Västmanland, SE-721 89 Västerås, and Centre for Clinical Research, Uppsala University, Central Hospital Västerås, SE-721 89 Västerås, Sweden

Key words: vestibular schwannoma, risk factors, cell phones, wireless phones, ionzing radiation

Introduction

Acoustic neuroma or vestibular schwannoma is a benign tumour in the eighth cranial nerve that leads from the inner ear to the brain. It is a slowly growing tumour in the auditory canal and expands gradually into the cerebellopontine angle with potential compression of vital brain stem centres. It tends to be encapsulated and grows in relation to the auditory and vestibular portions of the nerve. This tumour type does not undergo malignant transformation. Tinnitus and hearing problems are the usual first symptoms of acoustic neuroma. Although it is a benign tumour it may cause persistent disabling symptoms after treatment such as loss of hearing and tinnitus that severely affect the daily life.

Acoustic neuroma is a rare tumour. The average age-standardised incidence rates ranged during 1987-2007 from 6.1 per 1,000,000 in Finnish men to 11.6 in Danish men. Women in Sweden had the lowest average rate of 6.4 per 1,000,000 and the highest rate, 11.6, was found in Denmark (1). The incidence increased significantly during the time period 1987-2007 when all Nordic countries (Denmark, Finland, Norway and Sweden) and both genders were combined, +3.0% per year, 95% confidence interval (CI) = +2.1 to 3.9%.

The aetiology of acoustic neuroma is not well known. Risk factors such as exposure to ionising radiation during childhood (2) and loud noise (3) have been suggested. Neurofibromatosis 2 is one established risk factor for acoustic neuroma with 90-95% lifetime risk (4).

During calls when a wireless phone (mobile phone or cordless phone; DECT) is held close to the head the eighth cranial nerve is expected to receive relatively high exposure to radiofrequency electromagnetic fields (RF-EMF). Thus, there is a particular concern about increased risk for acoustic neuroma due to exposure to RF-EMF emissions during use of these devices. Results for long-term use of wireless phones and the risk for acoustic neuroma have been published by the Hardell group (5,6) and by the WHO Interphone study group; only mobile phone use was published for Interphone (7). Both sets of studies provided corroborative results, demonstrating an association between acoustic neuroma and exposure to RF-EMF from wireless phones. We have recently summarised and discussed these results (8,9).

In May 2011, the International Agency for Research on Cancer (IARC) at WHO evaluated the carcinogenic effect of RF-EMF on humans. The evaluation included radiation from mobile phones and from other devices that emit similar non-ionising electromagnetic fields. The conclusions stated that there were positive associations between exposure to radiofrequency radiation from wireless phones and glioma, and acoustic neuroma. It was concluded that RF-EMF is a Group 2B, i.e. a 'possible' human carcinogen (10,11).

In order to obtain results relating to longer-term use of wireless phones we decided to perform a new case-control study on brain tumours encompassing study subjects during the time period 2007-2009. The ethics committee also approved this new study.

The results for malignant brain tumours and meningioma are being published separately. This report presents the results for acoustic neuroma. Since the cases in this new study were few (n=73), we decided to make a pooled analysis for the two study periods 1997-2003 and 2007-2009.

Materials and methods

Wireless technology. Wireless technology has been used in Sweden since the early 1980s. Initially, analogue phones (NMT; Nordic Mobile Telephone System) were used, but this system was finally closed down in 2007. Since the early 1990s the market has been increasingly dominated by digital GSM phones. In 2003 the third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), was introduced in Sweden. Currently the fourth generation, 4G (Terrestrial 3G), is being established. Nowadays, mobile phones are used more than landline phones in Sweden (12). Worldwide, an estimated 5.9 billion mobile phone subscriptions were reported at the end of 2011 by the International Telecommunication Union (13).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since early 1990s using a digital 1900 MHz system. They are very common, overtaking telephones connected to landlines. These devices also emit RF-EMF radiation when used and should be given equal consideration with mobile phones when human health risks are evaluated.

Inclusion criteria. This report is based on results from two study periods, 1997-2003 and 2007-2009. The same methods were used for both periods including similar questions on use of mobile and cordless phones. All studies were of the case-control design and included both men and women who were alive. Cases were reported to us from the cancer registries. The diagnosis was based on histopathology in all cases. Tumour localisation (side of head) was based on reports to the cancer registries and medical records, which were obtained after informed consent from the patients.

Cases with both benign and malignant brain tumours were included in the study. For each case one control matched on age in 5-year groups and gender, living in the same geographical region as the respective case, was drawn from the population registry. They were assigned the same year as the diagnosis of the respective case as cut-off in assessment of exposure. All these controls were used in the analysis of the results for acoustic neuroma.

The results for the time period 1997-2003, which included the age group 20-80 years, have been published previously and further details can be found in these reports [Hardell *et al* (5,8,14)]. Cases and controls aged 20-80 years at the time of diagnosis living in certain geographical areas in Sweden, as presented in those publications, were included during that time period.

Our new study included cases aged 18-75 years at the time of diagnosis during 2007-2009. Again, the diagnosis was verified by histopathology in all cases. They were reported to us from cancer registries and the whole of Sweden was now included. For administrative reasons the Gothenburg region could only be included for the years 2008 and 2009.

For both study periods the responsible physician was contacted for permission before the case was included. Medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used for calculation of tumour volume.

Exposure assessment. The questionnaire was similar for both study periods. Use of wireless phones, i.e. both mobile and cordless phones, was assessed by a self-administered questionnaire supplemented by a phone interview. The questionnaire also contained a number of other questions on e.g. occupation, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionizing radiation. These questions were also supplemented over the phone by the interviewer. A structured protocol was used for all questions during the interviews.

The ear that had been most regularly used during calls with mobile and/or cordless phone was assessed by separate questions; >50% of the time for one side, or equally for both sides. The matched control was assigned the same side as the tumour of the respective case in the series of studies. The whole procedure was conducted without knowledge of exposure status. Use of the wireless phone was defined as ipsilateral (≥50% of the time) or contralateral (<50% of the time) in relation to tumour side.

Each questionnaire received a unique Id-number that did not disclose whether it was a case or a control. Thus, case or control status was not disclosed to the interviewer or during further data processing. All information was coded and entered into a database. Case or control status was not disclosed until the statistical analyses.

Statistical methods. All analyses were done using StataSE 12.1 (Stata/SE 12.1 for Windows; StataCorp., College Station, TX).

Table I. Odds ratio (OR) and 95% confidence interval (CI) for acoustic neuroma based on 316 cases and 3,530 controls.[a]

Latency	Analogue OR, CI (Ca/Co)	Digital (2G) OR, CI (Ca/Co)	Digital (UMTS, 3G) OR, CI (Ca/Co)	Mobile phone, total OR, CI (Ca/Co)	Cordless phone OR, CI (Ca/Co)	Digital type OR, CI (Ca/Co)	Wireless phone OR, CI (Ca/Co)
Acoustic neuroma (n=316)							
Total, >1 year	2.9	1.5	3.9	1.6	1.5	1.5	1.5
	2.0-4.3	1.1-2.1	0.4-35	1.2-2.2	1.1-2.1	1.1-2.0	1.1-2.0
	(86/558)	(173/2,014)	(7/141)	(200/2,148)	(156/1,724)	(216/2,393)	(227/2,472)
>1-5 years	2.2	1.4	4.1	1.3	1.5	1.4	1.2
	1.2-4.0	0.996-2.0	0.5-36	0.9-1.8	1.05-2.1	1.01-1.9	0.8-1.6
	(16/87)	(80/714)	(7/127)	(65/674)	(72/653)	(93/796)	(72/748)
>5-10 years	3.2	1.8	-	2.3	1.6	1.6	1.9
	2.0-5.2	1.1-2.8		1.6-3.3	1.1-2.5	1.1-2.3	1.3-2.7
	(33/137)	(56/659)	(0/14)	(77/688)	(60/655)	(73/758)	(84/767)
>10-15 years	3.0	1.8	-	2.1	1.4	1.6	2.0
	1.6-5.7	0.97-3.4		1.3-3.5	0.8-2.6	0.97-2.8	1.3-3.2
	(16/113)	(28/471)	(0/0)	(34/476)	(19/294)	(38/584)	(44/578)
>15-20 years	3.5	1.8	-	2.1	0.5	1.1	1.7
	1.5-8.5	0.8-4.2		1.02-4.2	0.1-2.1	0.5-2.5	0.9-3.3
	(9/107)	(9/170)	(0/0)	(12/196)	(2/109)	(9/242)	(13/253)
>20 years	7.7	-	-	4.5	6.5	8.1	4.4
	2.8-21			2.1-9.5	1.7-26	2.0-32	2.2-9.0
	(12/114)	(0/0)	(0/0)	(12/114)	(3/13)	(3/13)	(14/126)

[a]Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis including the whole control sample (i.e. matched to both malignant and benign cases) to increase the power of the study.

Latency period (time between first exposure and diagnosis) was defined using year of first use of a wireless phone and year of diagnosis (the same year for the matched control). The cumulative number of hours of use was calculated using number of years and average time used per day. Use in a car with external antenna was disregarded; so was use of a handsfree device. We adopted a minimum latency period of one year (≤1 year) for exposure, less than that was included in the unexposed category. The same year as for each case's diagnosis was used for the corresponding control as the cut-off for exposure accumulation. Note that latency was calculated separately for the respective phone type or combination of phones that were analysed.

Adjustment was made for the matching variables gender, age (as a continuous variable), and year of diagnosis. In addition, adjustment was made for socio-economic index (SEI) divided into four categories (blue-collar worker, white-collar worker, self-employed, no work), since an association between white-collar work and brain tumours has been reported (15). Latency was analysed using five time periods, >1-5 years, >5-10 years, >10-15 years, >15-20 years and >20 years. Cumulative use of the various phone types and combinations was analysed in quartiles based on the distribution of total use of wireless phones among the controls. Latency and cumulative use were also analysed as continuous variables (per year of latency, per 100 h cumulative use) to further explore the dose-response relations. Laterality was not analysed for the whole group of wireless phone users since the side could differ for mobile phone and cordless phone for the same person.

Restricted cubic splines were used to visualize the relationship between cumulative use and latency of wireless phones and acoustic neuroma. Adjustment was made for the same variables as in the logistic regression. Four knots were used at the 5th, 35th, 65 and 95th percentiles as suggested by Harrell (16). P-value for non-linearity was estimated by testing if the coefficient of the second and third spline was equal to zero, using the Wald test. Tumour volume was estimated using the ellipsoid formula:

$$\frac{4}{3}\ \pi\ (\frac{D_1}{2}\ \text{x}\ \frac{D_2}{2}\ \text{x}\ \frac{D_3}{2})$$

(D_1, D_2, D_3, diameters in the three axis). Change of tumour volume per year of latency and per 100 h of cumulative use was analysed using linear regression analysis, adjusted for age

 EXHIBIT A

Table II. Odds ratio (OR) and 95% confidence interval (CI) for acoustic neuroma, total, ipsilateral and contralateral exposure.[a]

	All			Ipsilateral			Contralateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue	86/558	2.9	2.0-4.3	54/252	2.9	1.9-4.6	29/184	2.5	1.4-4.2
Digital (2G)	173/2,014	1.5	1.1-2.1	108/865	1.7	1.1-2.4	62/684	1.3	0.9-2.1
Digital (UMTS, 3G)	7/141	3.9	0.4-35	3/70	1.9	0.2-20	3/45	3.6	0.3-38
Mobile phone, total	200/2,148	1.6	1.2-2.2	123/920	1.8	1.3-2.6	73/729	1.5	0.98-2.2
Cordless phone	156/1,724	1.5	1.1-2.1	101/766	1.8	1.2-2.6	52/565	1.2	0.7-1.8

[a]Numbers of exposed cases (Ca) and controls (Co) are displayed. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Ipsilateral, ≥50% use of the phone on the same side as the tumour was located. Contralateral, <50% use of the phone on the same side as the tumour was located.

Table III. Odds ratio (OR) and 95% confidence interval (CI) for dose-response between use of wireless phones and acoustic neuroma.[a]

Quartile	Analogue OR, CI (Ca/Co)	Digital (2G) OR, CI (Ca/Co)	Digital (UMTS, 3G) OR, CI (Ca/Co)	Mobile phone, total OR, CI (Ca/Co)	Cordless phone OR, CI (Ca/Co)	Digital type OR, CI (Ca/Co)	Wireless phone OR, CI (Ca/Co)
First quartile	2.5	1.5	9.1	1.6	1.2	1.3	1.2
	1.6-3.9	1.04-2.1	0.9-89	1.1-2.2	0.8-1.8	0.9-1.9	0.8-1.7
	(42/304)	(83/885)	(5/47)	(91/920)	(36/478)	(59/618)	(57/641)
Second quartile	3.1	1.2	1.5	1.5	1.6	1.3	1.5
	1.8-5.5	0.7-2.0	0.1-26	0.9-2.3	1.03-2.3	0.9-2.0	1.02-2.2
	(23/146)	(30/467)	(1/54)	(37/492)	(49/534)	(49/583)	(56/596)
Third quartile	4.2	2.2	2.7	2.4	2.1	1.9	1.9
	2.1-8.4	1.3-3.6	0.2-47	1.5-3.8	1.3-3.2	1.3-2.8	1.3-2.8
	(14/82)	(38/388)	(1/31)	(42/416)	(47/451)	(58/613)	(58/617)
Fourth quartile	6.6	2.1	-	2.6	1.9	2.1	2.2
	2.6-17	1.2-3.9		1.5-4.4	1.1-3.2	1.4-3.3	1.5-3.4
	(7/26)	(22/274)	(0/9)	(30/320)	(24/261)	(50/579)	(56/618)

[a]Numbers of exposed cases (Ca) and controls (Co) are displayed. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. First quartile, 1-122 h; second quartile, 123-511 h; third quartile, 512-1,486 h; fourth quartile, >1,486 h. p, trend: analogue, p=0.16; digital (2G), p=0.08; digital (UMTS, 3G), p=0.14; mobile phone, total, p=0.052; cordless phone, p=0.11; digital type, p=0.07; wireless phone, p=0.03.

and gender. The volumes were log-transformed to normalize the distribution. The percentage changes were calculated from the β coefficients in the model, using the expression: $(e^{\beta\text{-coefficient-1}}) \times 100$.

Results

Of the 338 cases with acoustic neuroma, 316 (93%) answered the questionnaire; 141 were men and 175 women. Of the 4,038 controls, 3,530 (87%) participated, 1,492 men and 2,038 women. The mean age was 52 years for cases (median 53, range 23-80) and 54 years for all controls (median 55, range 19-80).

Table I summarises the results for acoustic neuroma and use of wireless phones. Analogue phones yielded OR = 2.9, 95% CI = 2.0-4.3 increasing to OR = 7.7, 95% CI = 2.8-21 in the longest latency group >20 years.

Use of digital 2G phones yielded a total OR = 1.5, 95% CI = 1.1-2.1 with somewhat higher OR in the longest latency group >15 years. The results for digital 3G were based on low numbers with short latency period. Overall, mobile phone use gave a statistically significant increased risk with the highest risk in the longest latency group >20 years yielding OR = 4.5, 95% CI = 2.1-9.5.

Cordless phone use gave OR = 1.5, 95% CI = 1.1-2.1, with higher risk in the longest latency group >20 years with

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for acoustic neuroma per 100 h of cumulative use and per year of latency.[a]

	Per 100 h cumulative use		Per year of latency	
Type of phone	OR	95% CI	OR	95% CI
Analogue	1.049	1.022-1.076	1.098	1.062-1.136
Digital (2G)	1.008	0.998-1.018	1.043	0.998-1.089
Digital (UMTS, 3G)	0.915	0.724-1.157	0.992	0.670-1.468
Mobile phone, total	1.009	1.001-1.017	1.060	1.031-1.089
Cordless phone	1.007	0.998-1.016	1.028	0.992-1.065
Digital type	1.006	1.0001-1.013	1.035	1.0003-1.071
Wireless phone	1.008	1.002-1.014	1.056	1.029-1.085

[a]Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

OR = 6.5, 95% CI = 1.7-26, but based on low numbers. Wireless phone use overall gave OR = 1.5, 95% CI = 1.1-2.0 increasing with latency >20 years to OR = 4.4, 95% CI = 2.2-9.0.

Table II summarises the results for use of wireless phones in relation to tumour side. For all studied phone types except digital 3G, somewhat higher ORs were calculated for ipsilateral wireless phone use than for contralateral.

Cumulative use of wireless phones was analysed in quartiles (Table III). Note that for the various phone types the cumulative time was counted for use of the specific phone, but for the category 'mobile phones' all types of mobile phones were included, and for 'wireless phones' use of cordless phones was also included. In general, the highest ORs were found in the fourth quartile with >1,486 h cumulative use. Mobile phone use in the fourth quartile gave OR = 2.6, 95% CI = 1.5-4.4 (p trend = 0.052), cordless phone use yielded OR = 1.9, 95% CI = 1.1-3.2 (p trend = 0.11) and wireless phone use overall gave OR = 2.2, 95% CI = 1.5-3.4 (p trend = 0.03).

The highest increase in risk per 100 h cumulative use and per year of latency was found for analogue phones, OR = 1.049, 95% CI = 1.022-1.076 and OR = 1.098, 95% CI = 1.062-1.136, respectively (Table IV). There was a statistically non-significant increase for cordless phone use. The digital types of wireless phones gave statistically significantly increased risk per 100 h cumulative use, OR = 1.006, 95% CI = 1.0001-1.013, and per year of latency, OR = 1.035, 95% CI = 1.0003-1.071. Overall, use of wireless phones gave statistically signficant increased risks per 100 h of cumulative use and per year of latency.

Gender-specific analyses yielded similar results. Cumulative use of wireless phones gave OR = 2.9, 95% CI = 1.5-5.6 for men in the fourth quartile and OR = 1.9, 95% CI = 1.1-3.4 for women; thus the results for both genders were statistically significant with 95% CI overlapping ORs (data not shown).

Fig. 1 illustrates the results for cumulative use of wireless phones using the restricted cubic splines method. The sharpest increase in risk was seen up to approximately 3,000 h of cumulative use; up to 10,000 h the increase was less (p, non-linearity = 0.01). Fig. 2 demonstrates a linear relationship (p, non-linearity = 0.60) between increasing risk and latency

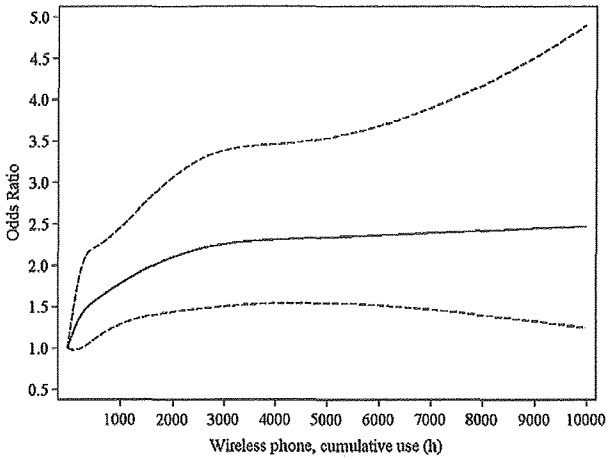


Figure 1. Restricted cubic spline plot of the relationship between cumulative use of wireless phones and acoustic neuroma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

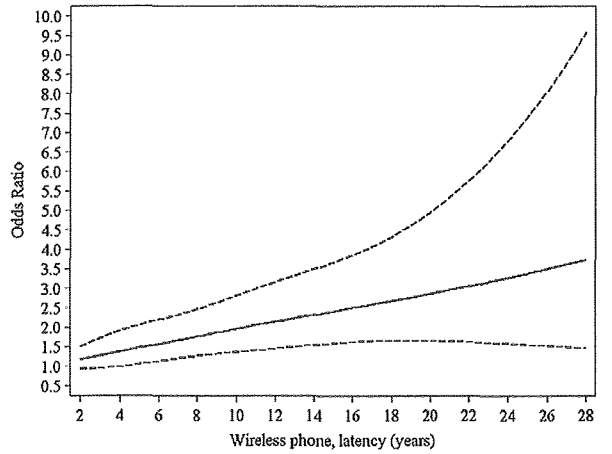


Figure 2. Restricted cubic spline plot of the relationship between latency of wireless phones and acoustic neuroma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Table V. Percentage change in tumour volume per year of latency and per 100 h of cumulative use.[a]

Type of phone	n	Change in volume per year of latency (%)	95% CI	p-value	Change in volume per 100 h of cumulative use (%)	95% CI	p-value
Analogue	61	+7.4	+1.0 to 14.2	0.02	+10.3	+2.4 to 18.7	0.01
Digital, 2G	116	+2.1	-4.1 to 8.6	0.52	+1.4	-0.6 to 3.5	0.18
Digital, UMTS, 3G	7	-	-	-	-	-	-
Mobile phone, total	137	+3.6	-1.1 to 8.6	0.13	+1.7	-0.1 to 3.5	0.06
Cordless phone	104	+4.2	-3.8 to 13.0	0.31	+1.2	-1.1 to 3.6	0.31
Wireless phone	153	+3.6	-1.1 to 8.6	0.13	+1.0	-0.1 to 2.2	0.08

[a]Adjustment was made for age at diagnosis and gender.

using data up to 28 years from first use of a wireless phone before tumour diagnosis.

For 218 cases with acoustic neuroma, tumour volume could be calculated on the basis of information in available CT/MRI reports. There was no statistically significant difference according to gender or age, although for cases aged >53 years (cut-off at median age) a somewhat larger volume was calculated than for lower age (median 4.2 versus 2.0 cm^3). Percentage tumour volume change per year of latency and per 100 h of cumulative use increased for all types of wireless phones and was statistically significant for analogue phones (Table V). The results for digital 3G phone was based on only seven cases so calculations were not meaningful.

Discussion

Main findings. The main result of this study was an association between use of wireless phones and acoustic neuroma. Increased risk was found for all studied phone types with the highest ORs in the longest latency period. Formally, the highest OR overall was calculated for digital mobile phones of the third generation (3G), but this was not statistically significant and was based on low numbers of exposed cases. Since this technology is rather new, data on long-term use are lacking.

It should be noted that most subjects had used several phone types. Increased risks were found for use of only analogue and only digital (2G) mobile phones (data not shown). Most of these calculations were hampered by numbers too low to permit meaningful interpretation of the results. Nevertheless, in the >10 year latency group, only analogue mobile phone use gave OR = 4.2, 95% CI = 0.8-21 and only digital 2G mobile phone use gave OR = 3.6, 95% CI = 1.2-11. The corresponding result for only cordless phone use was OR = 1.5, 95% CI = 0.3-7.3. A high risk was calculated for use of both mobile and cordless phones in the latency group >20 years yielding OR = 6.2, 95% CI = 2.8-14.

Most of the RF-EMF emissions from a handheld phone are absorbed on the side of the brain on which the phone is used (ipsilateral), with the highest dose in the area where acoustic neuroma develops (17). We found higher ORs for ipsilateral wireless phone use, but increased risks were also calculated for contralateral use. One contributing factor to the latter finding could be that hearing deficit is an early clinical sign of acoustic neuroma; the subjects might change the ear for phone use due to that circumstance.

In our present study, cumulative use of wireless phones was divided into quartiles depending on cumulative use of wireless phones overall among controls. For wireless phones the highest overall risk was found in the fourth quartile >1,486 h of cumulative use. This corresponds to approximately 25 min wireless phone use per day for 10 years. There was a statistically significant trend (p=0.03) for increasing cumulative use of wireless phones overall, but the trend was of borderline statistical significance for mobile phones (p=0.052). The OR showed a statistically significant increase per 100 h of cumulative use and per year of latency for both mobile and wireless phone use. Cordless phone use also increased the OR per 100 h of cumulative use and per year of latency.

Tumour volume increased per year of latency and per 100 h of cumulative use of wireless phones. The result was statistically significant for analogue phones, in accordance with overall findings of higher risk for use of that phone type. It should be noted that the increase in tumour volume was higher for ipsilateral use of mobile phones of the digital 2G type and for cordless phones than for contralateral use of the respective type. This ought to make the findings biologically more relevant (data not shown).

Strengths and limitations. In our new case-control study for the period 2007-2009 there were few cases with acoustic neuroma (n=73; eight did not participate). Statistical analysis of the results was less meaningful although the whole control sample (n=1,368) for the study period could be used. We decided to include our previous study period 1997-2003 and make a pooled analysis. Thus, 243 additional cases and 2,162 additional controls were included in the pooled analysis. This was justified by the fact that a similar questionnaire was used for both study periods. Assessment of use of both mobile and cordless phones was the same including the similar protocol for supplementary phone interviews regarding unclear facts or to verify exposures. Furthermore, in the statistical analysis, adjustment was made for year of diagnosis, gender, age and SEI-code.

Recall and observational bias might be an issue in case-control studies. We investigated in more detail the possibility of that in one of our previous studies (18). Reporting a previous cancer or if a relative helped to fill in the questionnaire did not

change the results. Potential observational bias during phone interviews was analysed by comparing change of exposure in cases and controls after these interviews. No statistically significant differences were found, showing that our results are unlikely to be explained by observational bias. To further validate exposure in the present study we used meningioma cases (n=1,624) as the referents to the acoustic neuroma cases (n=315). Similar results were found. Thus, wireless phone use gave in total (>1 year latency) OR = 1.4, 95% CI = 1.005-1.9, and in the latency group >20 years OR = 3.2, 95% CI = 1.5-6.8 with meningioma cases as referents. The corresponding results with population based controls were OR = 1.5, 95% CI = 1.1-2.0 and OR = 4.4, 95% CI = 2.2-9.0, respectively (Table I). These results clearly show that the results in this study can not be explained by recall or observational bias.

In our previous study on acoustic neuroma (5) a diagnostic head X-ray was associated with an overall increased risk; OR = 3.1, 95% CI = 2.2-4.2 (unpublished data). The risk increased to OR = 7.5, 95% CI = 3.4-16 for >3 occasions of X-ray investigations with >1 year latency. However, there was no interaction with mobile phone use (p=0.73), cordless phone use (p=0.95), or wireless phone use (p=0.81). In the present study X-ray investigations of the head were again assessed. These data are to be analysed further, but in view of our previous results an interaction with wireless phone use is unlikely.

Certainly some X-ray investigations might be tumour-related, but using >10 year latency, X-ray of the head gave OR = 4.9, 95% CI = 1.5-16, indicating it is a risk factor for acoustic neuroma. Dental X-ray investigations did not increase the risk for acoustic neuroma in the 1997-2003 time period study: OR = 0.6, 95% CI = 0.3-1.4 (n=236 cases, 2,124 controls; missing data for seven cases and 38 controls); there was no dose-response relationship. The literature on dental and head X-ray investigations and the risk for acoustic neuroma is scanty. In the German part of Interphone, medical ionising radiation gave OR = 0.97, 95% CI=0.54-1.75 for acoustic neuroma (19). In a study from Brazil on 44 acoustic neuroma patients and 104 controls, exposure to >1 cranial X-ray investigation gave OR = 4.55; 95% CI = 1.10-19.2 (20).

Frequent dental X-ray investigations were associated with an increased risk for acoustic neuroma encompassing 343 patients who underwent Gamma Knife surgery and 343 matched control patients with degenerative spinal disorders (21). Head and neck CT was associated with a statistically significantly decreased risk, which casts doubt on the study methods including selection of controls.

Loud noise has been suggested as a risk factor for acoustic neuroma (3). In the questionnaire we asked for exposure to 'extremely high noise', and the results are available for the study period 1997-2003. This gave OR = 1.4, 95% CI = 0.97-1.9, increasing somewhat to OR = 1.5, 95% CI = 1.01-2.2 in the >10 years latency group. However, there was no interaction with use of wireless phones (p=0.71) or the different phone types.

One strength of our whole study was that we included only cases with a histopathological diagnosis of a brain tumour. This was because we wanted a valid diagnosis of the brain tumour for separate analysis depending on tumour type. If necessary, the histopathological reports were supplemented by records from pathology departments around the country after informed consent from the subject. Thus, we were able to classify all brain tumours on the basis of WHO codes. Neurofibromatosis type II was identified in two cases with acoustic neuroma. Exclusion of these cases did not change the results.

Stereotactic radiosurgery is one option for treatment of acoustic neuroma, especially smaller ones (22,23). Obviously in these cases the diagnosis is made by CT and MRI without histopathology. However, exclusion of cases with only clinical diagnosis is unlikely to have biased the results, since criteria for treatment are not expected to be related to habits of wireless phone use.

One advantage of this study was the high response rate among both cases and controls. The response rate was 93% (n=316) among the finally included cases with acoustic neuroma. Of the controls, 87% (n=3,530) answered the questionnaire. In the Interphone study on acoustic neuroma (7) lower response rates were obtained for both cases and controls; see below. To ensure that results are as valid as possible, a high response rate is always necessary. In fact, non-responding controls in Interphone tended to be less frequent users of mobile phones than participating controls, leading to underestimation of the risk (24-26).

Results from other studies. A case-case study on acoustic neuroma and mobile phone use was conducted in Japan (27). The cases were identified during 2000-2006 at 22 participating neurosurgery departments. The diagnosis was based on histopathology or CT/MRI imaging. Of 1,589 cases 816 (51%) agreed to participate and answered a mailed questionnaire. A total of 787 cases were included in the final analysis. Two datasets were analysed, one comprising 362 cases with no tumour-related symptoms one year before diagnosis, and the other comprising 593 cases with no symptoms five years before diagnosis. Cases with ipsilateral mobile phone use were regarded as exposed and those with contralateral use were assumed to be unexposed and were treated as the reference category. Overall, no increased risk was found. However, for average daily call duration >20 min with reference date one year, risk ratio (RR) = 2.74, 95% CI = 1.18-7.85 increased to RR = 3.08, 95% CI = 1.47-7.41 with reference date five years before diagnosis. Unfortunately, no results were given for cumulative hours of use over the years. For cordless phones no increased risk was found but the analysis was not very informative.

In the Interphone study, 1,121 (82%) acoustic neuroma cases participated, range 70-100% by centre (7). Of the controls 7,658 (53%) completed the interviews, range 35-74% by centre. The final matched analysis (1:1 or 1:2) comprised 1,105 cases and 2,145 controls. Overall no increased risk was found censoring exposure at one year or at five years before the reference date, OR = 0.85, 95% CI = 0.69-1.04 and OR = 0.95, 95% CI = 0.77-1.17, respectively. Cumulative number of hours of ipsilateral mobile phone use ≥1,640 h up to one year before the reference date gave OR = 2.33, 95% CI = 1.23-4.40 and contralateral use OR = 0.72, 95% CI = 0.34-1.53 for acoustic neuroma (7). Cumulative number of hours of ipsilateral mobile phone use ≥1,640 hours up to five years before the reference date gave OR = 3.53, 95% CI = 1.59-7.82, and for

contralateral use OR = 1.69, 95% CI = 0.43-6.69. The risk increased further for cumulative ipsilateral use ≥1,640 h with start ≥10 years before the reference date to OR = 3.74, 95% CI = 1.58-8.83. Contralateral use in that group yielded OR = 0.48, 95% CI = 0.12-1.94; however, this was based on only four exposed cases and nine exposed controls. Overall, OR = 1.93, 95% CI = 1.10-3.38 was obtained for long-term use with start ≥10 years before the reference date and cumulative call time ≥1,640 h.

We conducted a meta-analysis on mobile phone use and its association with acoustic neuroma based on results by the Hardell group (5) and the Interphone study (7). The analysis was based on published results by Interphone since we do not have access to their database. Our results were recalculated to these exposure groups. A random-effects model was used based on a test for heterogeneity in the overall (≥10 years and ≥1,640 h) groups. For the latency group ≥10 years, the highest risk was obtained for ipsilateral use: OR = 1.81, 95% CI = 0.73-4.45. The risk increased further for cumulative use ≥1,640 h yielding OR = 2.55, 95% CI = 1.50-4.40 for ipsilateral use (8).

In the study by Han *et al* (21) regular mobile phone use was statistically significant more common among the cases (p=0.006). The adjusted OR for ≥10 years' mobile phone use was 1.29, 95% CI = 0.69-2.43 (crude OR = 2.20, 95% CI = 1.43-3.39). Regarding cordless phone use the adjusted OR for ≥10 years use was 1.07, 95% CI = 0.51-2.21 (crude OR = 1.40, 95% CI = 0.84-2.35). However, not all statistically significant confounders were included in the adjusted model (residency excluded) and no results were given for wireless phone use in total. The authors noted that they had insufficient information on mobile phone use. The results for cordless phones were not discussed in detail.

An increased risk for acoustic neuroma associated with reported use of mobile phone was found in a study from UK (28). Ever use gave in the 10+ years group RR = 2.46, 95% CI = 1.07-5.64 with increasing risk with duration of use (trend p=0.03). The study was limited by e.g. mobile phone use only at baseline, no details on handedness use, no information on tumour laterality and no assessment of use of cordless phones.

In conclusion, this study confirmed previous results of an association between use of mobile and cordless phones and acoustic neuroma. The risk increased with time since first use. For use of both mobile and cordless phones the risk was highest in the longest latency group. Tumour volume increased per 100 h of cumulative use and years of latency for wireless phones. Using the meningioma cases as reference entity gave similar results as with population based controls indicating that the results could not be explained by recall or observational bias.

Acknowledgements

The study from 2007-2009 was supported by grants from Cancer-och Allergifonden, Cancerhjälpen, Örebro University Hospital Cancer Fund, Pandora-Foundation for Independent Research, Berlin, Germany, and Gigaherz.ch, Schweizerische Interessengemeinschaft Elektrosmog-Betroffener, www.gigaherz.ch. We thank Ms. Iréne Larsson and Mrs. Margaretha Sjölund, for assistance in the data collection and Mr. Brian Stein for general support. The reporting of cancer patients from Oncology Centres in Sweden is acknowledged.

References

1. Larjavaara S, Feychting M, Sankila R, *et al*: Incidence trends of vestibular schwannomas in Denmark, Finland, Norway and Sweden in 1987-2007. Br J Cancer 105: 1069-1075, 2011.
2. Schneider AB, Ron E, Lubin J, *et al*: Acoustic neuromas following childhood radiation treatment for benign conditions of the head and neck. Neuro Oncol 10: 73-78, 2008.
3. Edwards CG, Schwartzbaum JA, Lönn S, Ahlbom A and Feychting M: Exposure to loud noise and risk of acoustic neuroma. Am J Epidemiol 163: 327-333, 2006.
4. Asthagiri AR, Parry DM, Butman JA, *et al*: Neurofibromatosis type 2. Lancet 373: 1974-1986, 2009.
5. Hardell L, Carlberg M and Hansson Mild K: Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997-2003. Int J Oncol 28: 509-518, 2006.
6. Hardell L and Carlberg M: Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol 35: 5-17, 2009.
7. Interphone Study Group: Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Cancer Epidemiol 35: 453-464, 2011.
8. Hardell L, Carlberg M and Hansson Mild K: Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 20: 85-110, 2013.
9. Hardell L, Carlberg M and Gee D: Mobile phone use and brain tumour risk: early warnings, early actions? In: Late Lessons from Early Warnings, part 2. European Environment Agency, Copenhagen, Denmark, 2013. http://www.eea.europa.eu/publications/late-lessons-2/late-lessons-chapters/late-lessons-ii-chapter-21/at_download/file. [Accessed 2013-04-12].
10. Baan R, Grosse Y, Lauby-Secretan B, *et al*: Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol 12: 624-626, 2011.
11. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-Ionizing radiation, Part 2: Radiofrequency Electromagnetic Fields Volume 102, IARC Press, Lyon, 2013. http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf [Accessed 2013-07-08].
12. Post- och Telestyrelsen. Svensk Telemarknad första halvåret 2011. http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf [Accessed 2013-04-13].
13. International Telecommunication Union, 2011. The World in 2011 - ICT Facts and Figures. http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf [Accessed 2013-04-13].
14. Hardell L, Carlberg M and Hansson Mild K: Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology 16: 113-122, 2009.
15. Preston-Martin S and Mack W: Neoplasms of the nervous system. In: Cancer Epidemiology and Prevention. Schottenfeld D and Fraumeni JF Jr (eds). Oxford University Press, New York, NY, pp1231-1281, 1996.
16. Harrell FE Jr: Regression Modeling Strategies. With Application to Linear Models, Logistic Regression and Survival Analysis. Springer, New York, NY, pp20-26, 2001.
17. Cardis E, Deltour I, Mann S, *et al*: Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 53: 2771-2783, 2008.
18. Hardell L, Hallquist A, Hansson Mild K, Carlberg M, Påhlson A and Lilja A: Cellular and cordless telephones and the risk for brain tumours. Eur J Cancer Prev 11: 377-386, 2002.
19. Blettner M, Schlehofer B, Samkange-Zeeb F, Berg G, Schlaefer K and Schüz J: Medical exposure to ionising radiation and the risk of brain tumours: Interphone study group, Germany. Eur J Cancer 43: 1990-1998, 2007.
20. Corona AP, Ferrite S, Lopes Mda S and Rêgo MA: Risk factors associated with vestibular nerve schwannomas. Otol Neurotol 33: 459-465, 2012.
21. Han YY, Berkowitz O, Talbott E, Kondziolka D, Donovan M and Lunsford LD: Are frequent dental X-ray examinations associated with increased risk of vestibular schwannoma? J Neurosurg 117 (Suppl): 78-83, 2012.

22. Litre F, Rousseaux P, Jovenin N, *et al*: Fractionated stereotactic radiotherapy for acoustic neuromas: a prospective monocenter study of about 158 cases. Radiother Oncol 106: 169-174, 2013.
23. Kondziolka D, Mousavi SH, Kano H, Flickinger JC and Lunsford LD: The newly diagnosed vestibular schwannoma: radiosurgery, resection, or observation? Neurosurg Focus 33: E8, 2012.
24. Vrijheid M, Cardis E, Armstrong BK, *et al*: Validation of short term recall of mobile phone use for the Interphone study. Occup Environ Med 63: 237-243, 2006.
25. Vrijheid M, Deltour I, Krewski D, Sanchez M and Cardis E: The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J Expo Sci Environ Epidemiol 16: 371-384, 2006.
26. Hardell L, Carlberg M and Hansson Mild K: Methodological aspects of epidemiological studies on the use of mobile phones and their association with brain tumors. Open Env Sci 2: 54-61, 2008.
27. Sato Y, Akiba S, Kubo O and Yamaguchi N: A case-case study of mobile phone use and acoustic neuroma risk in Japan. Bioelectromagnetics 32: 85-93, 2011.
28. Benson VS, Pirie K, Schüz J, *et al*: Mobile phone use and risk of brain neoplasms and other cancers: prospective study. Int J Epidemiol 2013; http://dx.doi:10.1093/ije/dyt072

INTERNATIONAL JOURNAL OF ONCOLOGY 00: 0-00, 0000

Case-control study of the association between malignant brain tumours diagnosed between 2007 and 2009 and mobile and cordless phone use

LENNART HARDELL[1], MICHAEL CARLBERG[1], FREDRIK SÖDERQVIST[1,3,4] and KJELL HANSSON MILD[2]

[1]Department of Oncology, University Hospital, SE-701 85 Örebro;
[2]Department of Radiation Physics, Umeå University, SE-901 87 Umeå, Sweden

DOI: 10.3892/ijo_xxxxxxxx

Abstract. Previous studies have shown a consistent association between long-term use of mobile and cordless phones and glioma and acoustic neuroma, but not for meningioma. When used these phones emit radiofrequency electromagnetic fields (RF-EMFs) and the brain is the main target organ for the hand-held phone. The International Agency for Research on Cancer (IARC) classified in May, 2011 RF-EMF as a group 2B, i.e. a 'possible' human carcinogen. The aim of this study was to further explore the relationship between especially long-term (>10 years) use of wireless phones and the development of malignant brain tumours. We conducted a new case-control study of brain tumour cases of both genders aged 18-75 years and diagnosed during 2007-2009. One population-based control matched on gender and age (within 5 years) was used to each case. Here, we report on malignant cases including all available controls. Exposures on e.g. use of mobile phones and cordless phones were assessed by a self-administered questionnaire. Unconditional logistic regression analysis was performed, adjusting for age, gender, year of diagnosis and socio-economic index using the whole control sample. Of the cases with a malignant brain tumour, 87% (n=593) participated, and 85% (n=1,368) of controls in the whole study answered the questionnaire. The odds ratio (OR) for mobile phone use of the analogue type was 1.8, 95% confidence interval (CI)=1.04-3.3, increasing with >25 years of latency (time since first exposure) to an OR=3.3, 95% CI=1.6-6.9. Digital 2G mobile phone use rendered an OR=1.6, 95% CI=0.996-2.7, increasing with latency >15-20 years to an OR=2.1, 95% CI=1.2-3.6. The results for cordless phone use were OR=1.7, 95% CI=1.1-2.9, and, for latency of 15-20 years, the OR=2.1, 95% CI=1.2-3.8. Few participants had used a cordless phone for >20-25 years. Digital type of wireless phones (2G and 3G mobile phones, cordless phones) gave increased risk with latency >1-5 years, then a lower risk in the following latency groups, but again increasing risk with latency >15-20 years. Ipsilateral use resulted in a higher risk than contralateral mobile and cordless phone use. Higher ORs were calculated for tumours in the temporal and overlapping lobes. Using the meningioma cases in the same study as reference entity gave somewhat higher ORs indicating that the results were unlikely to be explained by recall or observational bias. This study confirmed previous results of an association between mobile and cordless phone use and malignant brain tumours. These findings provide support for the hypothesis that RF-EMFs play a role both in the initiation and promotion stages of carcinogenesis.

Correspondence to: Dr Lennart Hardell, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden
E-mail: lennart.hardell@orebroll.se

Present addresses: [3]Department of Public Health and Community Medicine, County Council of Västmanland; [4]Centre for Clinical Research, Uppsala University, Central Hospital Västerås, SE-721 89 Västerås, Sweden

Key words: ipsilateral, 25-years latency, time since first exposure, glioma, wireless phones

Introduction

In May, 2011, the International Agency for Research on Cancer (IARC) at WHO evaluated the carcinogenic effect to humans from radiofrequency electromagnetic fields (RF-EMF). It included radiation from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields. It was concluded that RF-EMF is a group 2B, i.e. a 'possible' human carcinogen (1,2).

The IARC evaluation of mobile phones was based mainly on case-control studies from the Hardell group in Sweden and the IARC Interphone study. Both sets of studies provided corroborative results, demonstrating an association between two types of brain tumours, glioma and acoustic neuroma, with exposure to RF-EMF from wireless phones. There was no consistent pattern of an association within the studied latency period (time since first exposure) with the most common benign brain tumour, meningioma, suggesting specificity for these other tumour types. However, it should be noted that in Interphone a reduced risk was found for glioma among regular users of mobile phones but an increased risk was found in the highest cumulative exposure group, >1,640 h (3). Clearly an increased risk was found

using 1-1.9 years as reference entity (data not shown). The pros and cons in the Interphone study have been discussed in several articles, e.g. Hardell *et al* (4,5), Cardis and Sadetzki (6).

We first provide some background to the development of the wireless technology because of its relevance to understanding the nature of exposures and exposure assessments.

The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT, Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981, but closed down on 31 December, 2007; NMT 900 operated during 1986-2000.

The digital system (GSM, Global System for Mobile Communication) using dual band, 900 and 1,800 MHz, started to operate in 1991, and it now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900/2,100 MHz RF fields has been introduced worldwide in recent years, and in Sweden in 2003. Currently, the fourth generation, 4G (Terrestrial 3G), operating at 800/2,600 MHz, and Trunked Radio Communication (TETRA 380-400 MHz) are being established in Sweden and elsewhere in Europe. Nowadays mobile phones are used more than landline phones in Sweden (http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf). Worldwide, an estimate of 5.9 billion mobile phone subscriptions was reported at the end of 2011 by the International Telecommunication Union (http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since the early 1990s using a digital 1,900 MHz system. They are very common, overtaking phones connected to landlines. Also, these devices emit RF-EMF radiation when used and should be equally considered as mobile phones when human health risks are evaluated.

The old analogue phones in Sweden, the so called NMT, had an output power of 1 W and were very seldom down-regulated giving lower RF-EMF emissions when used since the distance between the base stations was several kilometers. The GSM phones are transmitting in a pulsed mode, active 1/8 of the time, and with a maximum output power of 2 W. This could be downregulated depending on the distance to the base stations. A typical mean value for the average output power is around 50-60 mW. The phone always starts the call with the maximum power before going down in power. The digital cordless phones operate in pulsed mode with a duty cycle of 1/24, the peak power is 250 mW. It is only the newer models that have regulation of the output power. The old ones always stayed with peak 250 mW, giving a time average of about 10 mW.

The absorption pattern, i.e. SAR values, associated with the phones is very different between different phones; some can give the peak value above the ear, some on the ear, and some even below the ear, see for instance Wilén *et al* (7). There are no known measurements of SAR for the cordless phones.

The first indication of an increased risk for brain tumours associated with the use of mobile phones was published more than 10 years ago (8). For tumours located in the temporal, occipital or temporoparietal lobe areas of the brain, an increased risk was found for ipsilateral mobile phone use. Exposure to radiation from wireless phones (mobile and cordless) is generally highest in the part of the brain that is near to the ear, the temporal lobe, on the same side of the head as the phone is generally held, ipsilateral exposure (9).

However, because these early results were based on low numbers of exposed people and different histopathological types of brain tumours, no firm conclusions could be drawn. Furthermore, this first study did not include the use of cordless phones (8,10). The next study from the Hardell group included cases diagnosed in the period 1997-2003, and was larger than the first study. This time, the use of cordless phones was also assessed. Further details may be found in the various publications that are based on the results from these studies (11-16).

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It was an international collaboration on brain tumour risk and mobile phone use, conducted under the aegis of IARC. Cases were diagnosed during 2000-2004, with slight variations in the different study regions (3,17). In contrast to the Hardell group studies, Interphone did not assess or present results for cordless phone use. These are the only studies to date that provide results for latency periods exceeding 10 years.

Exponential increases in access to and ownership of wireless phones in most countries has occurred since the end of the 1990s. Because the technology is relatively recent, results on health risks for long-term use, exceeding decades, are still lacking. Moreover, in Sweden the major increase in use (duration in minutes of calls) and exposure to radiation fields from these phones (not merely access to or ownership of) in the general population is most evident after 2003 (18).

To obtain results for longer exposure periods of wireless phone use, we conducted an entirely new study on brain tumours. In this article, we present the most recent results for malignant brain tumours. Updated results and discussions of this research area can be found elsewhere (5,19). The study was approved by the ethics committee: Regional Ethics Committee, Uppsala University; Uppsala, Sweden. DNR 2005:367.

Materials and methods

Case ascertainment. Sweden comprises six administrative medical regions each having a cancer registry; annually, these registries are linked to the national Swedish cancer register. The reporting to us of newly diagnosed brain tumour cases varied between these six regions, from once a month to once a year from one region (Umeå). In our previous studies covering the time period 1997-2003, we received reports on new cases as these arose, or one to two times per month. For logistical reasons, this was not possible in the present study for the different cancer registries.

Inclusion criteria. The inclusion criteria specified both men and women aged 18-75 years at the time of brain tumour diagnosis (ICD-7 code 193.0) during the period 2007 to 2009. Furthermore, the diagnosis had to be verified histopathology for all cases and only living cases were included in the study. The cases were reported to us from population-based cancer registries from across all regions of Sweden. For administrative reasons, the Gothenburg region could be included for only the years 2008 and 2009. All patients, both with a malignant

or a benign brain tumour, were included in the whole study. Once the inclusion criteria were satisfied, the attending physician was contacted for permission to include the case in the study. The present publication presents results for cases with a malignant brain tumour.

The Swedish Population Registry was used for identification of controls. One control matched on gender and in 5-year age groups was used for each case, both malignant and benign brain tumour cases. All controls were recruited from the same source population (residential) as the cases. Controls were only selected to the finally included living cases. They were assigned the same year as the diagnosis of the respective case as the cut-off in assessing exposure. Thus, the same methods were used as in our previous studies (12,13).

Exposure assessment. Use of wireless phones, both mobile and cordless, was assessed by a self-administered questionnaire supplemented over the phone. Both cases and controls received an introduction letter and were asked if they were willing to participate and answer the included questionnaire. To get as high response rate as possible two reminders were sent. All mobile phones in Sweden have had either prefix 010 (analogue type) or prefix 07 (digital type). Thus by asking for the prefix it was possible both to verify use of a mobile phone and the type. The questionnaire also contained a number of other questions on, for example, occupational history, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionizing radiation. All questions were supplemented over the phone by the interviewer at the same time. A structured protocol was used for all questions as a prompt. The written questionnaire was evaluated and further interviews were made according to the protocol. Most subjects were also phone interviewed to clarify different aspects in the questionnaire. There was no difference regarding supplementary interviews according to being a case (75% supplemented) or a control (70% supplemented). Adjusting for whether or not a supplementary interview was performed did not change the results of the logistic regression analysis.

The ear that had mostly been used during calls with mobile and/or cordless phones was assessed by separate questions; >50% of the time for one side, or equally much for both sides. After informed consent from the patients, medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used to define tumour localization. The matched control was assigned the same side as the tumour of the respective case using the same method as in previous studies (3,12,13,17). The whole procedure was blind to exposure status. Use of the wireless phone was defined as ipsilateral (>50% of the time), or contralateral (<50% of the time) in relation to tumour side.

All questionnaires received a unique identity number that did not indicate case or control status. Thus, the interviewer was blind to case or control status throughout data processing. The interviewers used a structured protocol that avoided questions that could reveal if the interviewee was a case or a control. All information was coded and entered into a database. A random sample of the questionnaires was coded twice by two independent persons with similar results. Being a case or control was revealed only during the statistical analyses.

Statistical methods. All analyses were done using StataSE 12.1. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis including the whole control sample (i.e. matched to both malignant and benign cases) to increase the power in the study. This was possible since adjustment/stratification was made for the two matching variables (gender, and age within 5 years).

The unexposed category consisted of people who reported no use of mobile or cordless phones, or a latency period <1 year (amount of time between first use of the phone and year of diagnosis). As noted earlier, the same year as for each case diagnosis was used for the corresponding control as the cut-off for exposure accumulation. Furthermore, because of the low number of unexposed cases, a further criterion was used, i.e. regardless of latency being <1 year, cumulative use <39 h (3rd percentile) of wireless phones in total among the controls was also used as cut-off for the referent group of 'no exposure' among cases and controls. The 3rd percentile was chosen to approximately correspond to one working week.

A latency period <1 year was used, as in our previous studies, to make it possible to analyse a late effect (promotion) in brain tumour genesis (12,13). Note that latency (time since first use until date of diagnosis) was calculated separately for the respective phone type or combination of phones that were analysed.

Latency was analysed using six time periods, >1-5 years, >5-10 years, >10-15 years, >15-20 years, >20-25 years and >25 years. Cumulative use of the phone types was analysed in quartiles based on use of wireless phones in total among the controls (first quartile >39-405 h, second quartile 406-1,091 h, third quartile 1,092-2,376 h, fourth quartile >2,376 h). Wald's test was performed to analyze the trend of the ORs across the quartiles of the phone types. Latency and cumulative use were also analysed as continuous variables (per year of latency, per 100 h cumulative use) to further explore the dose-response relations.

Adjustment was made for the matching variables gender, age (as a continuous variable) and year of diagnosis. In addition, adjustment was made for socio-economic index (SEI) divided into four categories (blue-collar worker, white-collar worker, self-employed, no work). Note that laterality of the tumour was not available for all cases, e.g., for midline tumours, or for tumours in both hemispheres (n=38). These were dropped from the laterality analysis together with controls (n=306) matched to cases without laterality data in the whole material. Laterality analysis was not made for the whole group of wireless phone users since the side differed for mobile phone and cordless phone for some of the included persons using both phone types (8.3% of the cases, 8.9% of the controls).

Restricted cubic splines were used to visualize the relationship between cumulative use and latency of wireless phones and malignant brain tumours. Adjustment was made for the same variables as in the logistic regression. Four knots were used at the 5th, 35th, 65th and 95th percentiles as suggested by Harrell (20). A p-value for non-linearity was estimated by testing if the coefficient of the second and third spline was equal to zero (20).

Most of the participating cases with a benign brain tumour (n=814) had meningioma (n=709). These results will be presented in another publication. As a further step to evaluate potential recall or observational bias the meningioma cases in the same study were used as the reference entity to the cases with malignant brain tumour, c.f. Hardell (21).

Table I. Descriptive data on the study sample of malignant brain tumour cases diagnosed between 2007 and 2009.

	Malignant
Reported from cancer registries	1,334
Deceased	520
Wrong diagnosis	18
Diagnosed other years	2
No address available	6
Language problems	2
Not capable to participate	47
No permission from physician	56
Total included	683
Refused to participate	90
Answered the questionnaire	593

Table II. Histopathology of all malignant brain tumours.

	Men		Women		Total	
Histopathology	n	%	n	%	n	%
Astrocytoma grade I-II	53	15.1	44	18.1	97	16.4
Grade I	6	1.7	5	2.1	11	1.9
Grade II	47	13.4	39	16.0	86	14.5
Astrocytoma grade III-IV	205	58.6	113	46.5	318	53.6
Grade III	30	8.6	15	6.2	45	7.6
Grade IV	175	50.0	98	40.3	273	46.0
Medulloblastoma	3	0.9	2	0.8	5	0.8
Oligodendroglioma	32	9.1	37	15.2	69	11.6
Ependymoma	10	2.9	9	3.7	19	3.2
Other/mixed glioma	39	11.1	23	9.5	62	10.5
Other malignant	8	2.3	15	6.2	23	3.9
All malignant	350		243		593	

Results

In Table I, the number of reported malignant cases from the regional cancer registries is shown. The largest numbers of cases excluded from the study were those who were 'deceased' (n=520), mostly with an astrocytoma WHO grade IV (glioblastoma multiforme). The implications of this exclusion are addressed below in the discussion section. The second largest group excluded was that with 'no permission from the treating physician' (n=56). Thus, of the 1,334 cases with a malignant tumour, 683 (51%) remained eligible for inclusion. Regarding cases with a benign brain tumour (n=814) these results are presented in separate articles; one on meningioma (22) one on acoustic neuroma (23).

Medical records and reports to the cancer registries were used to classify tumour histopathology. Of the 683 cases of malignancy, 593 (87%) answered the questionnaire; 350 were men and 243 women. In Table II, the various diagnoses of malignant brain tumours are shown. Most of the cases were diagnosed with a glioma (astrocytoma, oligodendroglioma, other/mixed glioma; n=546; 92%) with astrocytoma being the most common subtype (n=415; 76% of glioma).

For the total sample of 1,601 cases, an equal number of matched controls received a questionnaire. Note that one case had two tumours, astrocytoma grade IV and meningioma and another case had ependymoma and acoustic neuroma. Of the included controls, 1,368 (85%) answered the questionnaire, 564 were men and 804 women. The mean age was 52 years for cases with malignant brain tumour (median 55, range 18-75) and 55 years for all controls (median 58, range 19-75). Of the cases with meningioma 200 were men and 509 were women. The mean age was 57 years (median 59, range 23-75 years).

In Table III, the results are shown for all malignant brain tumours and use of wireless phones. Analogue phones yielded OR=1.8, 95% CI=1.04-3.3 increasing to OR=3.3, 95% CI=1.6-6.9 in the latency group of >25 years. Note that the latency time was counted from the first use of the specific telephone type; for instance, a 2G user may have used an analogue phone before.

Use of digital 2G phones gave an overall OR=1.6, 95% CI=0.996-2.7. In the latency group >1-5 years, an OR=1.8, 95% CI=1.01-3.4 was calculated. Lower ORs were obtained in the latency groups >5-10 years and >10-15 years increasing to an OR=2.1, 95% CI=1.2-3.6 with latency >15-20 years, which was the longest latency interval.

The results for digital 3G phones showed highest risk in the >5-10 years latency group, OR=1.6, 95% CI=0.5-4.9. This result was based on low numbers and no long-term users existed since this technology is new. One case and no control reported use of only a 3G phone.

A similar pattern as for digital 2G phones was found for use of cordless phones with increased risk in the shortest latency period, then dropping off and again increasing in the latency group >15-20 years to an OR=2.1, 95% CI=1.2-3.8. Only 6 cases and 13 controls reported use of cordless phone with latency >20-25 years, so these results are less reliable.

In Table III we also display results for all uses of digital phones (2G, 3G and/or cordless phone; 'digital type'). The pattern of an association was similar to 2G and cordless phones, with a statistically significant increased risk in the shortest latency period, then dropping off and again statistically significant increased risk in the latency group >15-20 years giving an OR=2.2, 95% CI=1.3-3.6.

We further show results for all wireless phone use combined. An increased risk was found overall with an OR=1.7, 95% CI=1.04-2.8, increasing in the shortest latency period >1-5 years to an OR=2.6, 95% CI=1.4-5.0, then decreasing somewhat with increasing latency; but with the highest risk is in the longest latency period >25 years with an OR=3.0, 95% CI=1.5-6.0.

In Table IV results are displayed when patients with meningioma in the same study are used as controls. The results were similar as in Table III using the population based controls. Most ORs were somewhat higher using meningioma cases as controls.

Overall, in Table V, ipsilateral use of analogue phones was associated with a higher risk, OR=2.3, 95% CI=1.2-4.5, than contralateral use, yielding OR=1.4, 95% CI=0.7-2.9. Ipsilateral use of digital 2G phones yielded a higher OR than contralateral use. Mobile phones overall for ipsilateral use, resulted in an OR=1.7, 95% CI=1.01-2.9; and for contralateral use, an OR=1.4, 95% CI=0.8-2.5. Ipsilateral use of cordless phones yielded an OR=1.9, 95% CI=1.1-3.2 compared with an OR=1.6, 95% CI=0.9-2.8 for contralateral use.

Table III. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours (n=593).

	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone		
Latency	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)
Total, >1 year	1.8	1.04-3.3	(144/260)	1.6	0.996-2.7	(546/1,208)	1.2	0.6-2.4	(67/140)	1.6	0.99-2.7	(548/1,217)	1.7	1.1-2.9	(461/1,015)	1.7	1.04-2.8	(571/1,261)	1.7	1.04-2.8	(571/1,261)
1-5 years	-		(0/0)	1.8	1.01-3.4	(42/109)	1.2	0.6-2.4	(55/126)	1.8	1.002-3.4	(41/108)	2.0	1.1-3.4	(102/209)	2.6	1.4-4.9	(33/63)	2.6	1.4-5.0	(32/61)
5-10 years	0.6	0.1-3.1	(2/10)	1.6	0.97-2.7	(213/477)	1.6	0.5-4.9	(12/14)	1.7	0.98-2.8	(190/423)	1.6	0.95-2.7	(188/436)	1.6	0.9-2.7	(177/421)	1.6	0.98-2.8	(163/378)
10-15 years	1.4	0.7-3.0	(25/51)	1.3	0.8-2.2	(187/453)	-		(0/0)	1.3	0.8-2.2	(163/399)	1.6	0.9-2.8	(108/248)	1.4	0.8-2.3	(212/523)	1.3	0.8-2.2	(184/466)
15-20 years	1.4	0.7-2.7	(39/86)	2.1	1.2-3.6	(104/169)	-		(0/0)	1.5	0.8-2.6	(76/174)	2.1	1.2-3.8	(57/109)	2.2	1.3-3.6	(143/241)	1.7	1.02-3.0	(110/231)
20-25 years	2.1	1.1-4.0	(48/80)	-		(0/0)	-		(0/0)	1.9	1.1-3.5	(48/80)	1.5	0.5-4.6	(6/13)	1.5	0.5-4.6	(6/13)	1.9	1.04-3.4	(52/92)
25 years	3.3	1.6-6.9	(30/33)	-		(0/0)	-		(0/0)	2.9	1.4-5.8	(30/33)	-		(0/0)	-		(0/0)	3.0	1.5-6.0	(30/33)

Unexposed latency ≤1 year; wireless phone use ≤39 h (3rd percentile). Number of exposed cases (Ca) and population based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Table IV. Odds ratio (OR) and 95 % confidence interval (CI) for malignant brain tumours (n=593) and meningioma cases (n=708) as reference entity.

	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone		
Latency	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)
Total, >1 year	2.2	1.1-4.1	(144/108)	1.8	1.1-3.2	(545/592)	2.3	0.9-5.7	(67/47)	1.8	1.1-3.2	(547/593)	1.8	1.03-3.1	(460/521)	1.8	1.1-3.1	(570/640)	1.8	1.1-3.1	(570/640)
1-5 years	-		(0/0)	1.7	0.9-3.4	(42/70)	2.4	0.96-6.1	(55/40)	1.7	0.9-3.4	(41/69)	2.0	1.1-3.7	(102/109)	2.1	1.05-4.3	(33/43)	2.1	1.04-4.3	(32/42)
5-10 years	1.1	0.1-8.3	(2/3)	2.0	1.1-3.5	(212/235)	1.4	0.3-6.0	(12/7)	1.9	1.1-3.4	(189/216)	1.7	0.96-3.0	(187/216)	1.8	1.05-3.2	(176/221)	1.9	1.05-3.3	(162/205)
10-15 years	2.0	0.8-4.9	(25/21)	1.5	0.9-2.7	(187/212)	-		(0/0)	1.5	0.8-2.7	(163/185)	1.6	0.9-2.8	(108/128)	1.5	0.9-2.7	(212/248)	1.4	0.8-2.5	(184/226)
15-20 years	1.8	0.8-3.7	(39/39)	2.3	1.2-4.3	(104/75)	-		(0/0)	1.8	0.9-3.3	(76/78)	2.1	1.1-4.1	(57/61)	2.2	1.2-3.9	(143/121)	1.9	1.1-3.4	(110/115)
20-25 years	2.4	1.1-5.2	(48/29)	-		(0/0)	-		(0/0)	2.5	1.2-5.2	(48/29)	1.0	0.3-3.6	(6/7)	1.1	0.3-3.8	(6/7)	2.1	1.05-4.2	(52/36)
25 years	3.0	1.3-7.4	(30/16)	-		(0/0)	-		(0/0)	3.1	1.3-7.1	(30/16)	-		(0/0)	-		(0/0)	3.1	1.3-7.0	(30/16)

Unexposed latency ≤1 year; wireless phone use ≤39 h (3rd percentile). Number of exposed cases (Ca) and controls (Co) are given. One subject with both a malignant brain tumor and a meningioma was excluded from the analysis. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Table V. Odds ratio (OR) and 95 % confidence interval (CI) for malignant brain tumours, total, ipsilateral and contralateral exposure.

	All			Ipsilateral			Contralateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue	144/260	1.8	1.04-3.3	84/118	2.3	1.2-4.5	46/84	1.4	0.7-2.9
Digital (2G)	546/1,208	1.6	0.996-2.7	322/530	1.7	1.02-2.9	190/404	1.4	0.8-2.5
Digital (UMTS, 3G)	67/140	1.2	0.6-2.4	38/69	1.2	0.5-2.8	24/45	1.1	0.4-3.1
Mobile phone, total	548/1,217	1.6	0.99-2.7	324/534	1.7	1.01-2.9	190/407	1.4	0.8-2.5
Cordless phone	461/1,015	1.7	1.1-2.9	272/454	1.9	1.1-3.2	156/327	1.6	0.9-2.8

Ipsilateral, >50% use of the phone on the same side as the tumour was located. Contralateral, <50 % use of the phone on the same side as the tumour was located. Tumor laterality not available for 38 cases and 306 controls. Number of exposed cases (Ca) and population based controls (Co) for ever use of the phone type according to exposure criteria are displayed. Note that the subjects could have used more than one phone type. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

Cumulative use of wireless phones was analysed in quartiles based on use of wireless phones in total among the controls, see Table VI. Note that for the various phone types, the cumulative time was counted for use of the specific phone, but for the category 'mobile phones' all types of mobile phones were included, and for 'wireless phones' also use of cordless phones was included. For all phone types and combinations thereof, the highest ORs were found in the fourth quartile, see Table VI. Thus, for analogue phones, an OR=7.7, 95% CI=2.5-24 (p-trend=0.01) was calculated, although based on low numbers. The digital (2G) phone yielded an OR=3.2, 95% CI=1.8-5.6 (p-trend <0.0001) in the same category. Also, UMTS (3G) resulted in an increased risk with an OR=5.1, 95% CI=0.8-32 (p-trend=0.28); but based on low numbers. The fourth quartile of cumulative cordless phone use yielded an OR=3.1, 95% CI=1.8-5.5 (p-trend <0.0001). Wireless phone use overall resulted in an OR=2.5, 95% CI=1.5-4.2 (p-trend=0.0001) in the fourth quartile with >2,376 h of cumulative use.

The ORs increased to statistically significant per 100 h of cumulative use for all types of phones except for UMTS (3G) with borderline significance, see Table VII. In a multivariate analysis including all phone types (i.e. analogue, 2G, 3G and cordless phone) similar results were found although not statistically significant for analogue phones (OR=1.015, 95% CI=0.996-1.034; data not shown). Wireless phone use increased the risk with an OR=1.009, 95% CI=1.006-1.012 per 100 h of cumulative use, Table VII. The risk increased also per additional year of latency, mostly for analogue phones, OR=1.044, 95% CI=1.019-1.070. These results did not change if years of use of any mobile or cordless phone prior to the respective type was included as a covariate in each analysis of the individual phone types (data not shown). Wireless phones overall yielded OR=1.018, 95% CI=1.001-1.036.

In Table VIII, results are presented for malignant brain tumours localized in the temporal lobe or overlapping temporal and adjacent lobe. Higher risk estimates were obtained than for the overall results. Thus, mobile phone use in the latency group >25 years resulted in an OR=4.8, 95% CI=1.7-14 compared with an OR=2.9, 95% CI=1.4-5.8 overall (see Table III for comparison). Cordless phone use in the group with the longest latency, >20-25 years, resulted in an OR=3.3, 95% CI=0.8-14 in the temporal lobe versus an OR=1.5, 95% CI=0.5-4.6 overall, although based on low numbers. Also, for overall wireless phone use, the highest OR was found among those with the longest latency, >25 years, with an OR=5.1, 95% CI=1.8-15 for tumours in the temporal lobe.

In Table IX, results are displayed for use of only one type of wireless phone. Regarding analogue phones, all cases and controls had also used other phone types. Use of only digital 2G types resulted in the highest risk in the shortest latency period >1-5 years with an OR=3.4, 95% CI=1.2-9.5. The risk decreased somewhat with longer latency, but increased again in the longest latency group >15-20 years to an OR=1.8, 95% CI=0.6-4.9. A similar risk pattern was found for use of cordless phones only, with even higher risk estimates, although based on low numbers in the longest latency groups. Use of wireless phones of only the digital type (2G, 3G, cordless phone) yielded an OR=1.7, 95% CI=1.01-2.7 overall, increasing to an OR=2.7, 95% CI=1.4-5.3 in the latency group >1-5 years. A decreased risk was seen with the longer latency period, but, again, it increased with latency >15-20 years to an OR=1.9, 95% CI=1.1-3.4.

Most types of malignant brain tumours were glioma (n=546). Separate analysis of that group of tumours gave similar results as for the whole group of malignant brain tumours. Mobile phone use with latency >25 years resulted in an OR=2.8, 95% CI=1.4-5.7 (data not shown). Also, for cordless phone use, the results were similar as in the overall analysis. Thus, with a latency >15-20 years, an OR=1.9, 95% CI=1.05-3.5 was found.

Fig. 1 illustrates the results for cumulative use of wireless phones using the restricted cubic splines method. There was a linear increasing trend of the risk up to 10,000 h (p, non-linearity=0.52). Fig. 2 demonstrates a borderline statistically significant non-linear relationship for the risk and latency using data up to 28 years from first use of a wireless phone before tumour diagnosis (p, non-linearity=0.05). Highest risk was found with longest latency. This finding gives support for RF-EMFs to play a role in the initiation and promotion stages of carcinogenesis.

Discussion

Main results and latency (time since first exposure) effects. The main result of this study was a statistically significant increased risk for malignant brain tumours associated with use of wireless phones, OR=1.7, 95% CI=1.04-2.8. The risk increased further in the latency group >1-5 years, but lower ORs were found in the latency groups >5-10 years and >10-15 years. With longer latency periods, the OR increased

Table VI. Malignant brain tumours (n=593).

	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone		
Quartile	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)
First	1.7	0.9-3.0	(90/184)	1.4	0.8-2.3	(202/620)	1.1	0.5-2.4	(35/87)	1.4	0.8-2.3	(190/587)	1.3	0.8-2.2	(164/434)	1.5	0.9-2.5	(113/327)	1.5	0.9-2.5	(108/317)
Second	1.6	0.8-3.4	(22/47)	1.9	1.1-3.3	(138/260)	1.0	0.4-2.6	(16/34)	1.7	1.02-3.0	(126/261)	1.7	1.01-3.0	(120/278)	1.4	0.8-2.4	(113/320)	1.4	0.8-2.4	(110/314)
Third	2.6	1.2-6.0	(18/23)	1.4	0.8-2.5	(84/199)	1.7	0.6-4.8	(11/17)	1.5	0.9-2.7	(95/210)	2.1	1.2-3.7	(98/194)	1.7	1.01-2.9	(139/317)	1.7	1.003-2.9	(137/315)
Fourth	7.7	2.5-24	(14/6)	3.2	1.8-5.6	(122/129)	5.1	0.8-32	(5/2)	2.8	1.6-4.8	(137/159)	3.1	1.8-5.5	(79/109)	2.6	1.5-4.3	(206/297)	2.5	1.5-4.2	(216/315)

Odds ratio (OR) and 95% confidence interval (CI) for cumulative use of wireless phones in quartiles based on use of wireless phones among controls in total. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used. First quartile >39-405 h; second quartile 406-1,091 h; third quartile 1,092-2,376 h; fourth quartile >2,376 h. p-trend (Wald's test): analogue, p=0.01; digital (2G), p<0.0001; digital (UMTS, 3G), p=0.28; mobile phone, total, p=0.0001; cordless phone, p<0.0001; digital type, p<0.0001; wireless phone, p=0.0001.

Table VII. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours per 100 h cumulative use and per year of latency.

	Per 100 h cumulative use		Per year of latency	
	OR	95% CI	OR	95% CI
Analogue	1.037	1.014-1.060	1.044	1.019-1.070
Digital (2G)	1.012	1.007-1.017	1.013	0.989-1.037
Digital (UMTS, 3G)	1.031	0.988-1.076	1.043	0.894-1.216
Mobile phone, total	1.011	1.006-1.015	1.016	0.999-1.034
Cordless phone	1.013	1.007-1.020	1.014	0.992-1.036
Digital type	1.010	1.006-1.013	1.016	0.994-1.039
Wireless phone	1.009	1.006-1.012	1.018	1.001-1.036

Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

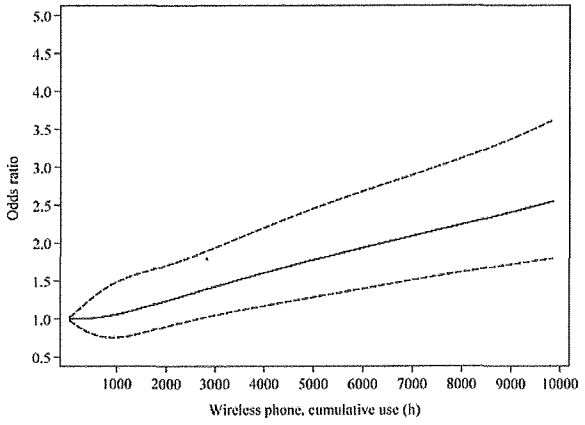


Figure 1. Restricted cubic spline plot of the relationship between cumulative use of wireless phones and malignant brain tumours. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

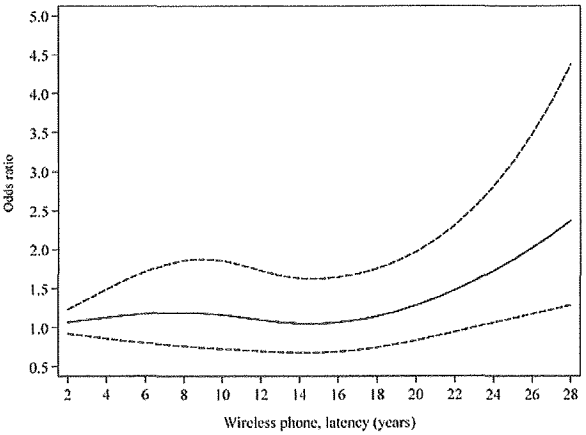


Figure 2. Restricted cubic spline plot of the relationship between latency of wireless phones and malignant brain tumours. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

Table VIII. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours located in temporal (n=161) and overlapping lobes [temporofrontal (n=31), temporoparietal (n=22), temporooccipital (n=13)]; in total n=227.

	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone			Digital type			Wireless phone		
Latency	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)
Total, >1 year	2.4	0.9-6.1	(67/260)	2.4	0.99-5.6	(211/1208)	1.7	0.5-5.9	(17/140)	2.3	0.99-5.6	(212/1217)	2.5	1.04-6.0	(175/1015)	2.5	1.05-5.9	(221/1261)	2.5	1.05-5.9	(221/1261)
1-5 years	-		(0/0)	3.3	1.2-8.7	(19/109)	1.6	0.5-5.9	(14/126)	3.1	1.2-8.4	(18/108)	3.0	1.2-7.6	(41/209)	4.4	1.6-12	(15/64)	4.5	1.6-13	(14/61)
5-10 years	0.9	0.1-9.1	(1/10)	2.4	0.96-5.7	(79/477)	2.1	0.3-14	(3/14)	2.4	0.97-5.8	(69/423)	2.2	0.9-5.4	(68/436)	2.4	0.99-5.9	(68/420)	2.4	0.98-5.9	(60/378)
10-15 years	1.6	0.5-5.3	(11/51)	1.8	0.7-4.3	(69/453)	-		(0/0)	1.6	0.7-4.1	(57/399)	2.3	0.9-5.7	(41/248)	1.8	0.8-4.5	(77/523)	1.8	0.7-4.4	(66/466)
15-20 years	1.7	0.6-5.0	(18/86)	3.0	1.2-7.4	(44/169)	-		(0/0)	2.0	0.8-5.2	(31/174)	2.8	1.05-7.4	(21/109)	3.0	1.2-7.4	(57/241)	2.3	0.9-5.8	(42/231)
20-25 years	2.6	0.9-7.2	(21/80)	-		(0/0)	-		(0/0)	2.7	1.02-7.3	(21/80)	3.3	0.8-14	(4/13)	3.4	0.8-14	(4/13)	2.7	1.04-7.2	(23/92)
25 years	5.1	1.7-16	(16/33)	-		(0/0)	-		(0/0)	4.8	1.7-14	(16/33)	-		(0/0)	-		(0/0)	5.1	1.8-15	(16/33)

Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis. Population based controls were used.

further with highest risk in the latency group >25 years, OR=3.0, 95% CI=1.5-6.0. From Table III, analogue mobile phones produced a risk increasing with latency, with the highest risk in the latency group >25 years. The OR increased statistically significantly per year of latency, see Table VII. A different pattern was seen for digital wireless phones, both the mobile and cordless types. The risk was higher in the short latency group >1-5 years, then dropped off and increased again with >15 years of latency. Regarding digital 3G mobile phones no conclusions could be drawn. The technique is new and no subject had latency >10 years.

No case or control had used a digital mobile phone with latency >25 years. Only 6 cases and 13 controls had used a cordless phone with latency >20-25 years, so the results for cordless phones with longest latency time were less reliable. Only one case had used only a 3G phone, so firm conclusions about the risk with 3G mobile phone use are not possible from this study. Regarding the use of digital 2G mobile and cordless phones, the OR increased per year of latency with statistically borderline significance. This was explained by the fact that the risk increase was U-shaped in relation to latency period. A further illustration is given in the restricted cubic spline plot showing a borderline statistically significant non-linear relationship, see Fig. 2.

Regarding long-term use of wireless phones and the association with brain tumours, it has not been possible to study longer latency periods than >10 years previously since the technology is too recent. This is the first study to examine effects with a latency time >25 years. This was for analogue phones. Regarding digital 2G mobile phones, the longest duration of latency was >15-20 years. The longest latency for use of cordless phones was >20-25 years with few subjects in that category. The results in this study indicate an early effect in brain tumour genesis seen both for analogue and digital phones, an initiator. Regarding digital phones, we found also a late effect in tumour development, a promoter.

Of interest is that we found that the risk was elevated among those who reported using only digital 2G mobile phones and only cordless phone, see Table IX. The risk was even higher for the use of only cordless phones, a fact that is of importance since all studies other than those from the Hardell group have not paid attention to such use. Including the use of cordless phones in the 'unexposed group' would have biased risk estimates towards unity, as discussed elsewhere (4,5).

Cumulative use. Cumulative use of wireless phones in our present study was divided into quartiles based on cumulative use of wireless phones overall among controls. For all phone types, the highest risk was found in the fourth quartile >2,376 h of cumulative use. This corresponds to about 40 min of wireless phone use per day for 10 years. There was a statistically significant trend for the different phone types, mobile phone use overall, and wireless phones overall. An especially elevated OR was calculated for analogue phone use, OR=7.7, 95% CI=2.5-24, in the fourth quartile. Also, 3G mobile phone use resulted in increasing risk, highest in the fourth quartile, but based on low numbers and no statistically significant trend (p=0.28). These results are also reflected in Table VII, with statistically significant increasing risk per 100 h of cumulative use for all phone types, except for 3G with borderline statistical significance. A

Table IX. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours (n=593).

	Analogue			Digital (2G)			Digital (UMTS, 3G)			Mobile phone, total			Cordless phone		
Latency	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)	OR	CI	(Ca/Co)
Total, >1 year	-		(0/0)	1.6	0.9-2.9	(78/176)	-		(1/0)	3.5	1.6-7.8	(23/44)	1.7	1.01-2.7	(427/1001)
1-5 years	-		(0/0)	3.4	1.2-9.5	(9/13)	-		(1/0)	5.8	2.0-17	(10/14)	2.7	1.4-5.3	(32/61)
5-10 years	-		(0/0)	1.6	0.8-3.2	(33/79)	-		(0/0)	3.7	1.3-11	(9/19)	1.7	1.03-3.0	(162/370)
10-15 years	-		(0/0)	1.3	0.6-2.6	(28/68)	-		(0/0)	2.0	0.4-9.4	(3/8)	1.3	0.8-2.2	(163/418)
15-20 years	-		(0/0)	1.8	0.6-4.9	(8/16)	-		(0/0)	2.9	0.2-39	(1/2)	1.9	1.1-3.4	(68/140)
20-25 years	-		(0/0)	-		(0/0)	-		(0/0)	-		(0/1)	0.6	0.1-2.7	(2/12)
25 years	-		(0/0)	-		(0/0)	-		(0/0)	-		(0/0)	-		(0/0)

Number of exposed cases (Ca) and population based controls (Co) are given. Results are given for use of only a specific phone type or use of both mobile and cordless phones. Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

linear relationship between cumulative use of wireless phones and the risk for malignant brain tumours is given in Fig. 1.

Consistency with our previous research. Clearly, digital mobile and cordless phones increase the risk of malignant brain tumours in our present study, as well as in our previous studies. For use of digital type wireless phones only, we found an OR=1.7, 95% CI=1.01-2.7. This finding is consistent with our previous result for the study period 1997-2003. Use of digital mobile and cordless phones yielded an OR=1.4, 95% CI=1.1-1.8 in that study (13). Further analysis in our previous study on use of only mobile phones yielded for glioma increased risk in the >10 year latency group, OR=2.6, 95% CI=1.7-4.1. For use of only cordless phones, an increased risk was found in the >5-10 years latency group, OR=1.9, 95% CI=1.3-2.9, whereas the result for >10 year latency was based on rather small numbers (5,15).

Furthermore, it should be noted that for the study period 1997-2003, we found an increased risk of malignant brain tumours in the latency period >5-10 years for users of wireless phones of the digital type. Thus, digital 2G phones yielded an OR=1.7, 95% CI=1.2-2.2, and for cordless phones, an OR=1.5, 95% CI=1.1-2.0 in that latency group (13). These risks increased further in the latency group >10 years, which was the longest time of wireless phone use in that study. This pattern was different for use of analogue phones, with statistically significant risk only in the group with a latency >10 years, giving an OR=2.4, 95% CI=1.6-3.4, a similar finding to that in the present study.

In summary, our results are consistent with an early effect in carcinogenesis (initiator) by analogue mobile phones, and both an early (initiator) and late (promoter) effect by wireless phones of the digital type.

Comparison with other studies, e.g. Interphone. In Interphone (data not shown), a statistically significant increased risk for glioma was seen in the group 2-4 years for regular use, with 1-1.9 years use as reference category, OR=1.68, 95% CI=1.16-2.41 (3). The highest OR was found in the 10+ years category for regular use, OR=2.18, 95% CI=1.43-3.31. Results were not presented according to type of mobile phone used. Overall, cumulative use >1,640 h in the shortest latency group of 1-4 years before reference date resulted in an increased risk, OR=3.77, 95% CI=1.25-11.4.

The highest absorption of RF-EMF emissions from a handheld phone is on the same side of the brain (ipsilateral) as the phone is used (9). Highest dose is absorbed in the temporal lobe of the brain. In previous studies, we have found risk being highest for ipsilateral wireless phone use (5,13). In Interphone, cumulative call time of mobile phones >1,640 h, resulted in glioma in the temporal lobe with an OR=1.87, 95% CI=1.09-3.22, and for ipsilateral mobile phone use, an OR=1.96, 95% CI=1.22-3.16 (3). Likewise, in our present study, the OR was higher for ipsilateral use of mobile or cordless phones, see Table V, and for malignant brain tumours in the temporal and overlapping lobes, see Table VIII.

A mean duration of mobile phone use of 2.8 years was reported in a study from USA (24). Overall, no increased risk was found for malignant brain tumours, except for a rare type, neuroepithelioma with OR=2.1, 95% CI=0.9-4.7. The type of mobile phone was not reported. No increased risk for glioma overall or in different groups of duration of regular use, at most >5 years, was reported in another study from USA (25). The type of mobile phone used was not published. An increased risk for glioma with short duration of analogue mobile phone use (1-2 years) was seen in a Finnish study, whereas no increased risk was found for digital phones (26). These results were based on low numbers. Cordless phone use was included in the 'unexposed' category in these studies, which is of interest to note since we have found an association with such phone use as reported above.

In a record linkage study from Denmark mobile phone subscribers from January 1, 1982, until December 31, 1995, were identified from the computerized files of the two Danish operating companies, TeleDenmark Mobil and Sonofon, which partly also funded the study. It has produced four articles that we have made a thorough review of (27). We concluded that its many limitations - embedded in the study design from the very beginning and mainly related to poor exposure assessment - cloud the findings of the four reports to such an extent that render them uninformative, at best. The Danish cohort study was included in the IARC evaluation of RF-EMF but the conclusion was that 'phone provider, as a surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment' (1). Thus, the Danish cohort study is uninformative as to cancer risks from mobile phone use.

Strengths and limitations. The present study included cases of malignant brain tumours diagnosed during 2007-2009 from across Sweden. For the cases diagnosed during 1997-2003 in our previous study (5), the prevalence of use of mobile phones was highest in the age group 30-54 years for men, and 35-54 years for women. Thus, we included the age group 18-75 years in this study to allow for the longest possible latency time (28). This is in contrast to the Interphone study, which included cases aged 30-59 years. Glioma is the most common malignant brain tumour, and the most common glioma subtype is astrocytoma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75% of all astrocytoma, in this study 66% of the cases with astrocytoma. The peak incidence is between 45-75 years, with a mean age of 61 years and with 80% older than 50 years (29). Thus, limiting the upper age to 59 years for cases as in Interphone (3) would diminish the possibility of finding an increased risk for the long-term use of mobile phones.

Recall and observational bias might be an issue in case-control studies. We investigated in more detail the possibility of that in one of our previous studies (11). Reporting a previous cancer or if a relative helped to fill in the questionnaire did not change the results. Potential observational bias during phone interviews was analysed by comparing the results based on exposure assessment before and after additional phone interviews. The results were similar with no statistically significant differences, showing that our results were unlikely to be explained by observational bias (11).

To further validate exposure in the present study we used meningioma cases as the referents, see Table IV. Thereby the results were similar to those obtained using the population based controls with consistency of the main findings for the main phone types, see Table III. It should be mentioned that a similar method was used previously on the controversy of cancer risks from certain chemicals. Based on clinical observations an increased risk for soft-tissue sarcoma (30) and malignant lymphoma (31) was postulated for exposure to phenoxyacetic acids, chlorophenols and contaminating dioxins. These bed-side observations were followed by case-control studies confirming an association, e.g. Hardell and Sandström (32), Hardell *et al* (33). Using colon cancer cases as referents yielded similar results as when population based controls were used, that is the increased risks were unlikely to be explained by recall or observational bias (21). Thus, similar conclusions can be made in the present study.

In our previous studies, we included only living cases so as to be able to solicit as good an assessment of exposure as possible (10,13). Especially side of head mostly used during phone calls would be difficult to assess using proxy interviews. Excluding deceased cases might, theoretically, bias the results, notably if there is no association between use of wireless phones and brain tumour in that patient group or even a protective effect. We, therefore, did a separate case-control study on deceased cases diagnosed during 1997-2003 with a malignant brain tumour in our previous studies (13) using deceased controls. Relatives of both groups were interviewed and we were able to confirm an increased risk for use of mobile phones (15,34). Thus, inclusion of only living cases and controls in this study would not likely bias the results away from unity.

In total, 1,334 cases were reported from the cancer registries covering all of Sweden. From the Gothenburg region, it was possible to get reports only of cases diagnosed during 2008 and 2009 for administrative reasons. However, exclusion of cases diagnosed during 2007 could not conceivably have biased the results. It has been published that the reporting of new brain tumour cases to the Swedish cancer registry is insufficient (35,36). It is, however, not likely that such omission from our study of not reported cases would be related to the status of being a user or not of wireless phones.

The majority of the cases with a histopathological brain tumour diagnosis that were excluded from this study were deceased (n=520; 39%). As mentioned above we have found an association with use of wireless phones also among the deceased cases (34). Furthermore, for glioma we have found an increased hazard ratio (HR) for survival (37). This was based on all glioma cases, both alive and deceased at the time of the studies as presented in Hardell *et al* (15). An increased hazard ratio was found for >10 years latency for both mobile phone use, HR=1.3, 95% CI=1.0005-1.6, and cordless phone use, HR=1.3, 95% CI=0.9-1.9. HR increased also with the cumulative number of hours of mobile and cordless phone use, with statistically significant trend for tertiles (p=0.01) of use of both phone types. For glioblastoma multiforme (WHO grade IV) use with >10 years latency for mobile phones increased the ratio, HR=1.3, 95% CI=0.9-1.7, and cordless phone, HR=1.8, 95% CI=1.2-2.8, indicating decreased survival for long-term and high cumulative use of wireless phones.

Most of the deceased cases in the present study had a diagnosis of glioblastoma multiforme, WHO grade IV. The median survival in that patient group is less than one year (38). We have reported a higher risk for mobile phone use for high grade glioma (WHO grades III-IV) than for low grade glioma (WHO-grades I-II) (5). Hence, the exclusion of deceased cases with glioblastoma multiforme with poor prognosis in this study might actually have biased the risk estimates towards unity.

We included only cases with a histopathological diagnosis of a brain tumour. We asked the six regional cancer registries not to report cases with only a clinical diagnosis. The reason was that we wanted to insure a confirmed diagnosis of the brain tumour for separate analyses for each tumour type. If necessary, we supplemented the histopathological reports with records from pathology departments around the country after informed consent from the respective case. Thus, we were able to classify all brain tumours based on WHO codes, see Table II. It is not probable that exclusion of cases with only a clinical diagnosis would have biased the results. We checked the Swedish Cancer Registry for the total number of patients with a brain tumour during the study period in the relevant age group. In total, 2,553 patients aged 20-74 years with a brain tumour were reported to the Swedish Cancer Registry versus 2,310 aged 20-74 years with a diagnosis based on histopathological diagnosis in our present study. This is in good agreement with expected numbers since, during 2007-2009, roughly 90% of brain tumour diagnoses in the Swedish Cancer Register were based on histology (http://www.socialstyrelsen.se/statistik/statistikdatabas).

An advantage of this study was the fairly high response rate among both cases and controls. The response rate was 87% (n=593) among the eligible cases. Of the controls, 85% (n=1,368) participated. These response rates were similar to those in our previous studies on malignant brain tumours, 85%

(n=1,251) among cases and 84% (n=2,438) among controls (5). Lower response rates were obtained in the Interphone study, namely 64%, range by centre 36-92%, (n=2,765) for glioma cases, and 53%, range 42-74%, (n=7,658) for controls (3). To obtain the most valid results possible, it is always necessary to have the highest possible response rate. In fact, not responding controls in Interphone tended to be less frequent users of mobile phones than participating controls, leading to an underestimation of the risk (4,39,40).

Our study was not designed to include a mini-interview on the use of wireless phones among non-responding cases and controls as done in parts of the Interphone study; we had no ethics clearance for that. Certainly, it would have been of value to verify the use of mobile phones by operator data on the phone traffic. We had no possibility to do this since we did not obtain valid information on the operator used over the years in spite of asking. Furthermore, use of cordless phones, an important source of RF-EMF exposure, is not possible to validate by operator data.

Statistical considerations. In view of the fact that practically everybody is using a wireless phone of some type today, it is not possible to obtain a large enough 'unexposed' group for meaningful statistical calculations. We, therefore, in addition to a latency <1 year, used the 3rd percentile (39 h) of cumulative time as a cut-off. Another option to obtain more 'unexposed' individuals would have been to change the cut-off for latency. However, doing this would limit the possibility of studying a late effect (promotion) in brain tumour genesis. Furthermore, it is difficult to find users that have been using only one single technology, i.e. NMT, GSM, UMTS, etc. Most users have used several technologies, and those with 3G phones who reported such use may have been unaware that the phone might have been operating on a 2G net for voice, if that was available. The analysis must be viewed with these facts in mind.

In the unconditional logistic regression analysis, all controls, both to cases with malignant and benign brain tumours, were used so as to maximise the statistical power. Analysis using conditional logistic regression yielded overall for wireless phones OR=2.1, 95% CI=1.1-3.7 versus OR=1.7, 95% CI=1.04-2.8 using unconditional logistic regression, see Table III. Using unconditional logistic regression only with controls matched to the malignant cases yielded overall for wireless phones OR=2.0, 95% CI=1.1-3.5. Similar differences were seen for the different phone types i.e. slightly higher risk estimates using conditional logistic regression or unconditional logistic regression with matched controls, although with wider confidence intervals. The latter was due to the fact that only controls matched to malignant cases could be included and also because only discordant matched pairs are considered in a conditional logistic regression analysis. The considerably smaller material would limit the possibility of performing several of the subgroup analyses in this article using this method. Using unconditional logistic regression analysis was possible since adjustment was made for the matching variables of age, gender and year of diagnosis. In addition, adjustment was made for socio-economic index since an association between white-collar work and brain tumours has been reported (41). Not adjusting for any of these variables yielded for wireless phone overall crude OR=2.2, 95% CI=1.4-3.5. No statistically significant interactions were found between the adjustment factors and wireless phone use. In our previous study, we found that heredity and previous X-ray investigations of the head increased the risk for glioma. However, these were independent risk factors with no interaction with use of wireless phones (16). Thus, it was not necessary to adjust for these risk factors in the present study.

More women than men were included as controls. This was because all controls in the study were included in the analysis. Among the cases with benign brain tumour, meningioma was about 2.5 times more common among women than men, an expected number. Thus, adjustment for gender was necessary.

Biological mechanisms. There is no generally accepted mechanism by which RF-EMF exposure produces changes in DNA. The energy level associated with exposure is too low to cause direct DNA strand breaks and DNA crosslinks. However, DNA damage can be caused by cellular biochemical activities such as free radicals. Several studies indicate that RF-EMFs increase free radical activity in cells (42,43). This process is probably mediated via the Fenton reaction. Hydrogen peroxide is converted into hydroxyl free radicals that are potent cytotoxic molecules. This reaction is catalyzed by iron. High levels of iron are found in metabolic active cells such as cancer cells as well as in cells undergoing abnormal proliferation, but also in brain cells. Glia cells might turn cancerous from DNA damage.

In a recently published study, it was demonstrated that RF-EMF exposure induced the formation of oxidative base damage in a mouse spermatocyte-derived cell line (44). This was mediated by reactive oxygen species (ROS) production. To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α-tocopherol pretreatment to antagonize the oxidation of ROS; α-tocopherol is an important lipophilic chain-breaking antioxidant that can inactivate harmful ROS. The protective role of α-tocopherol pretreatment confirmed that ROS are involved in RF-EMF exposure-induced DNA base damage (44). These findings support the idea that low energy RF-EMF that is insufficient to directly induce DNA strand breaks may nonetheless produce genotoxic effects in the form of DNA base damage.

We know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in a large series of tumours of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma (45). Thus, since the natural history of most glioma cases, from earliest events to clinical manifestation, is unknown but, most likely requires several decades, the exposure duration has in most studies been incompatible with a tumour initiating effect. This is the first study with long-term use of wireless phones. Interestingly, the most elevated OR was found in the latency group >25 years use. We also found results indicating a late effect on tumour development (promotion).

Initiation and promotion have different effects on the incidence of brain tumours. An initiating effect would have the most direct effect on the incidence. Our results indicate that such an effect would be apparent after more than a 20-year use of mobile phones, and thus be too early to be found in cancer registries. On the other hand, if the exposure acts as a promoter, this would decrease latency time for already existing

tumours, giving a temporary, but not a continuous, increase in incidence. In addition, it must be noted that any such effect on tumour development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumour type (28).

In conclusion, this study confirmed previous results of an association between use of mobile and cordless phones and malignant brain tumours. The risk was highest for ipsilateral use and tumours in the temporal lobe. The results are consistent with initiation carcinogenesis for analogue phones, and both initiation and promotion carcinogenesis for digital wireless phones.

Acknowledgements

We thank Ms. Iréne Larsson and Mrs. Margaretha Sjölund, for assistance in the data collection and Mr. Brian Stein for general support. Colin L. Soskolne, Professor Emeritus (Epidemiology), University of Alberta, Canada, and Adjunct Professor, Faculty of Health, University of Canberra, Australia, provided helpful editorial assistance in the writing of this article. The study was supported by grants from Cancer- och Allergifonden, Cancerhjälpen, Örebro University Hospital Cancer Fund, Pandora-Foundation for Independent Research, Berlin, Germany, and Gigaherz.ch, Schweizerische Interessengemeinschaft Elektrosmog-Betroffener, www.gigaherz.ch. The reporting of cancer patients from the Oncology Centres in Sweden is acknowledged.

References

1. Baan R, Grosse Y, Lauby-Secretan B, *et al*: Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol 12: 624-626, 2011.
2. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part 2: Radiofrequency electromagnetic fields. Volume 102. IARCPress, Lyon, 2013. http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf. Accessed July 11, 2013.
3. Interphone Study Group: Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol 39: 675-694, 2010.
4. Hardell L, Carlberg M and Mild KH: Methodological aspects of epidemiological studies on the use of mobile phones and their association with brain tumors. Open Env Sciences 2: 54-61, 2008.
5. Hardell L, Carlberg M and Mild KH: Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 20: 85-110, 2013.
6. Cardis E and Sadetzki S: Indications of possible brain tumour risk in mobile phone studies: should we be concerned? Occup Environ Med 68: 169-171, 2011.
7. Wilén J, Sandström M and Mild KH: Subjective symptoms among mobile phone users - a consequence of absorption of radiofrequency fields? Bioelectromagnetics 24: 152-159, 2003.
8. Hardell L, Mild KH, Påhlson A and Hallquist A: Ionizing radiation, cellular telephones and the risk for brain tumours. Eur J Cancer Prev 10: 523-529, 2001.
9. Cardis E, Deltour I, Mann S, *et al*: Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 53: 2771-2783, 2008.
10. Hardell L, Näsman Å, Påhlson A, Hallquist A and Mild KH: Use of cellular telephones and the risk for brain tumours: A case-control study. Int J Oncol 15: 113-116, 1999.
11. Hardell L, Hallquist A, Mild KH, Carlberg M, Påhlson A and Lilja A: Cellular and cordless telephones and the risk for brain tumours. Eur J Cancer Prev 11: 377-386, 2002.
12. Hardell L, Carlberg M and Mild KH: Case-control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000-2003. Environ Res 100: 232-241, 2006.
13. Hardell L, Carlberg M and Mild KH: Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997-2003. Int Arch Occup Environ Health 79: 630-639, 2006.
14. Hardell L, Carlberg M and Mild KH: Epidemiological evidence for an association between use of wireless phones and tumor diseases. Pathophysiology 16: 113-122, 2009.
15. Hardell L, Carlberg M and Mild KH: Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. Int J Oncol 38: 1465-1474, 2011.
16. Carlberg M and Hardell L: On the association between glioma, wireless phones, heredity and ionising radiation. Pathophysiology 19: 243-252, 2012.
17. Interphone Study Group: Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Cancer Epidemiol 35: 453-464, 2011.
18. Post-och Telestyrelsen. Svensk Telemarknad 2010. http://www.statistik.pts.se/pts2011/FILES/RAPPORTER/2010/Telemarknad_2010.pdf. Accessed July 11, 2013.
19. Hardell L, Carlberg M and Gee D: Mobile phone use and brain tumour risk: early warnings, early actions? In: Late Lessons from Early Warnings, Part 2. European Environment Agency, Copenhagen, 2013. http://www.eea.europa.eu/publications/late-lessons-2/late-lessons-chapters/late-lessons-ii-chapter-21/at_download/file. Accessed July 11, 2013.
20. Harrell FE Jr: Regression Modeling Strategies. With Application to Linear Models, Logistic Regression and Survival Analysis. Springer, New York, NY, pp20-26, 2001.
21. Hardell L: Relation of soft tissue sarcoma, malignant lymphoma, and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health 7: 119-130, 1981.
22. Carlberg M, Söderqvist F, Mild KH and Hardell L: Meningioma patients diagnosed 2007-2009 and the association with use of mobile and cordless phones: a case-control study. Environ Health 12: 60, 2013.
23. Hardell L, Carlberg M, Söderqvist F and Mild KH: Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997-2003 and 2007-2009 and use of mobile and cordless phones. Int J Oncol 43: 1036-1044, 2013.
24. Muscat JE, Malkin MG, Thompson S, *et al*: Handheld cellular telephone use and risk of brain cancer. JAMA 284: 3001-3007, 2000.
25. Inskip PD, Tarone RE, Hatch EE, *et al*: Cellular-telephone use and brain tumors. N Engl J Med 344: 79-86, 2001.
26. Auvinen A, Hietanen M, Luukkonen R and Koskela RS: Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology 13: 356-359, 2002.
27. Söderqvist F, Carlberg M and Hardell L: Review of four publications on the Danish cohort study on mobile phone subscribers and risk of brain tumours. Rev Environ Health 27: 51-58, 2012.
28. Kundi M: Essential problems in the interpretation of epidemiologic evidence for an association between mobile phone use and brain tumours. C R Physique 11: 556-563, 2010.
29. Ohgaki H, Dessen P, Jourde B, *et al*: Genetic pathways of glioblastoma: a population-based study. Cancer Res 64: 6892-6899, 2004.
30. Hardell L: Soft-tissue sarcoma and exposure to phenoxy acids - A clinical observation. Läkartidningen 74: 2853-2854, 1977 (In Swedish).
31. Hardell L: Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet 1: 55-56, 1979.
32. Hardell L and Sandström A: Case-control study: soft-tissue sarcomas and exposure to phenoxyacetic acids or chlorophenols. Br J Cancer 39: 711-717, 1979.
33. Hardell L, Eriksson M, Lenner P and Lundgren E: Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 43: 169-176, 1981.
34. Hardell L, Carlberg M and Mild KH: Mobile phone use and the risk for malignant brain tumors: a case-control study on deceased cases and controls. Neuroepidemiology 35: 109-114, 2010.
35. Bergenheim T, Malmström A, Bolander H, *et al*: Registration on regional basis of patients with primary brain tumors. Regional differences disclosed. Läkartidningen 104: 332-341, 2007 (In Swedish).

36. Barlow L, Westergren K, Holmberg L and Talbäck M: The completeness of the Swedish Cancer Register: a sample survey for year 1998. Acta Oncol 48: 27-33, 2009.
37. Hardell L and Carlberg M: Use of mobile and cordless phones and survival of patients with glioma. Neuroepidemiology 40: 101-108, 2013.
38. Ohgaki H and Kleihues P: Population-based studies on incidence, survival rates, and genetic alterations in astrocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 64: 479-489, 2005.
39. Vrijheid M, Cardis E, Armstrong BK, *et al*: Validation of short term recall of mobile phone use for the Interphone study. Occup Environ Med 63: 237-243, 2006.
40. Vrijheid M, Deltour I, Krewski D, Sanchez M and Cardis E: The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk. J Expo Sci Environ Epidemiol 16: 371-384, 2006.
41. Preston-Martin S and Mack W: Neoplasms of the nervous system. In: Cancer Epidemiology and Prevention. Schottenfeld D, Fraumeni JF Jr (eds). Oxford University Press, New York, NY, pp1231-1281, 1996.
42. Lai H and Singh NP: Melatonin and a spin-trap compound block radiofrequency electromagnetic radiation-induced DNA strand breaks in rat brain cells. Bioelectromagnetics 18: 446-454, 1997.
43. Phillips JL, Singh NP and Lai H: Electromagnetic fields and DNA damage. Pathophysiology 16: 79-88, 2009.
44. Liu C, Duan W, Xu S, *et al*: Exposure to 1800 MHz radiofrequency electromagnetic radiation induces oxidative DNA base damage in a mouse spermatocyte-derived cell line. Toxicol Lett 218: 2-9, 2013.
45. Collins VP: Gliomas. Cancer Surv 32: 37-51, 1998.

EXHIBIT C

Environmental Health

BioMed Central
The Open Access Publisher

Meningioma patients diagnosed 2007--2009 and the association with use of mobile and cordless phones: a case--control study

Environmental Health 2013, **12**:60 doi:10.1186/1476-069X-12-60

Michael Carlberg (michael.carlberg@orebroll.se)
Fredrik Söderqvist (fredrik.soderqust@ltv.se)
Kjell Hansson Mild (kjell.hansson.mild@radfys.umu.se)
Lennart Hardell (lennart.hardell@orebroll.se)

ISSN 1476-069X

Article type Research

Submission date 24 May 2013

Acceptance date 16 July 2013

Publication date 19 July 2013

Article URL http://www.ehjournal.net/content/12/1/60

Meningioma patients diagnosed 2007–2009 and the association with use of mobile and cordless phones: a case–control study

Michael Carlberg[1*]
[*] Corresponding author
Email: michael.carlberg@orebroll.se

Fredrik Söderqvist[1,2,3]
Email: fredrik.soderqust@ltv.se

Kjell Hansson Mild[4]
Email: kjell.hansson.mild@radfys.umu.se

Lennart Hardell[1]
Email: lennart.hardell@orebroll.se

[1] Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden

[2] Department of Public Health and Community Medicine, County Council of Västmanland, SE-721 89 Västerås, Sweden

[3] Centre for Clinical Research, Uppsala University, Central Hospital Västerås, SE-721 89 Västerås, Sweden

[4] Department of Radiation Physics, Umeå University, SE-90187 Umeå, Sweden

Abstract

Background

To study the association between use of wireless phones and meningioma.

Methods

We performed a case–control study on brain tumour cases of both genders aged 18–75 years and diagnosed during 2007–2009. One population-based control matched on gender and age was used to each case. Here we report on meningioma cases including all available controls. Exposures were assessed by a questionnaire. Unconditional logistic regression analysis was performed.

Results

In total 709 meningioma cases and 1,368 control subjects answered the questionnaire. Mobile phone use in total produced odds ratio (OR) = 1.0, 95% confidence interval (CI) = 0.7-1.4 and cordless phone use gave OR = 1.1, 95% CI = 0.8-1.5. The risk increased statistically significant per 100 h of cumulative use and highest OR was found in the fourth quartile

(>2,376 hours) of cumulative use for all studied phone types. There was no statistically significant increased risk for ipsilateral mobile or cordless phone use, for meningioma in the temporal lobe or per year of latency. Tumour volume was not related to latency or cumulative use in hours of wireless phones.

Conclusions

No conclusive evidence of an association between use of mobile and cordless phones and meningioma was found. An indication of increased risk was seen in the group with highest cumulative use but was not supported by statistically significant increasing risk with latency. Results for even longer latency periods of wireless phone use than in this study are desirable.

Keywords

Case–control study, 25 years latency, Benign brain tumour, Meningioma, Wireless phones

Background

Meningioma is the most common benign brain tumour and accounts for about 30% of intracranial tumours [1]. It develops from the pia and arachnoid membrane that cover the central nervous system. Meningioma is an encapsulated, well-demarcated and rarely malignant tumour. It is slowly growing and gives neurological symptoms by compression of adjacent structures. Headaches and seizures are common symptoms. This tumour type is most common among middle-aged and elderly persons. There are more women than men that develop meningioma and the incidence is about two fold higher in women than men [2,3].

Ionizing radiation is a well-established risk factor with time interval to tumour development of decades [4,5]. Sex hormones have been suggested to be of importance due to the female predominance but the role is not clear. A cohort study in Finland showed an increased risk of meningioma among postmenopausal women with ever use of estradiol-only medicine [6]. However, it has been suggested that sex hormone differences can not fully explain the higher incidence in women [7]. What the study actually shows is that the hormone receptor status does not differ between male and female meningioma. Obviously, since women have higher levels of circulating estrogens this will cause a larger growth rate and consequently a higher incidence of meningioma. In our previous study on meningioma and use of wireless phones [8] intake of oral contraceptives was no risk factor, (odds ratio (OR) = 1.0, 95% confidence interval (CI) = 0.8-1.3), whereas somewhat increased risk was found for estrogen intake (OR = 1.2, 95% CI = 0.97-1.5), to be published. We further analysed hormone treatment that started $\leq$ 50 years of age or > 50 years of age (approximate age of menopause) without statistically significant decreased or increased risks. The analyses were based on 916 meningioma cases and 2162 controls, cf Hardell et al. [8].

During the recent decade there has been an increase in access and ownership of wireless phones in most countries. When used they emit radiofrequency electromagnetic fields (RF-EMF). The brain is the main target organ during use of the handheld phone [9]. Thus, fear of an increased risk for brain tumours has dominated the debate during the last one or two decades. The GSM (Global System for Mobile Communication) phones and to a lesser extent the cordless phones emit also extremely low frequency magnetic field from the battery when used [10,11].

In May 2011 the International Agency for Research on Cancer (IARC) at WHO evaluated the carcinogenic effect to humans from RF-EMF. It included radiation from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields in the frequency range 30 kHz – 300 GHz. It was concluded that RF-EMF is a Group 2B, i.e. a 'possible', human carcinogen [12,13]. The IARC decision on mobile phones was based mainly on results for glioma and acoustic neuroma in case–control studies from the Hardell group from Sweden [8,14,15] and the IARC Interphone study [16].

The IARC Working Group found for meningioma that the available evidence was insufficient to reach a conclusion on an association with mobile phone use [12]. The only studies that gave results for 10 years latency or more were those from the Hardell group [8,17] and the Interphone study group [16].

The results for meningioma as well as for other types of brain tumours are so far based on limited numbers of long-term users since the technology is fairly new. In Sweden the major increase in use (minutes of outgoing calls) and exposure to radiation fields from these phones (not merely access or ownership) in the general population is most evident after 2003 [18].

In order to get results for longer time period for use of wireless phones we decided to perform a new case–control study. Here results for benign brain tumours are presented. Updated results and discussions of this research area can be found elsewhere [19,20].

Methods

Wireless technology

The wireless technology has been used in Sweden since the early 1980's. First analogue phones (NMT; Nordic Mobile Telephone System) were used, but this system was finally closed down in 2007. The market has since early 1990's increasingly been dominated by the digital GSM phones (2G; second generation of mobile phones). In 2003 the third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), was introduced in Sweden. Currently the fourth generation, 4G (Terrestrial 3G), is established. Nowadays mobile phones are used more than landline phones in Sweden [21]. Worldwide, an estimate of 5.9 billion mobile phone subscriptions were reported at the end of 2011 by the International Telecommunication Union [22].

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800–900 MHz RF fields, but since early 1990's using a digital 1 900 MHz system. They are very common and are overtaking telephones connected to landlines. Also these devices emit RF-EMF radiation when used and should be equally much considered as mobile phones when human health risks are evaluated.

Inclusion criteria

Our new study included both men and women aged 18–75 years at the time of brain tumour diagnosis (ICD-7 code 193.0) during 2007–2009. The diagnosis was verified by histopathology for all cases. All were alive when included in the study. They were reported to us from cancer registries and the whole of Sweden was included. For administrative reasons the Gothenburg region could only be included for the years 2008 and 2009. Sweden contains

six administrative medical regions with cancer registries, which each year are linked together to the national Swedish cancer register. The reporting to us of new diagnoses of brain tumour cases varied between these six regions from once a month to once a year from one region (Umeå).

Before inclusion in the study we checked that the criteria for participation were fulfilled. After that the responsible physician was contacted for permission to include the case in the study. In Table 1 the numbers of reported cases with a benign brain tumour are displayed, in total 1,039 subjects. Of these 920 (89%) were included in the study according to the inclusion criteria.

Table 1 Descriptive data on the study sample of cases with benign brain tumour diagnosed during 2007–2009

	Benign
Reported from cancer registries	1,039
Deceased	31
Wrong diagnosis	28
Diagnosed other years	1
No address available	5
Language problems	5
Not capable to participate	20
No permission from physician	29
Total included	920
Refused to participate	106
Answered the questionnaire	814

The Swedish Population Registry was used for identification of controls. One control matched on gender and age in 5-year groups was used to each case, both with a malignant or a benign brain tumour. All controls were recruited from the same source population as the cases as soon as the treating physician had permitted inclusion of the respective case. The whole country was used for retrieving controls (Gothenburg region excluded 2007). They were assigned the same year as the diagnosis of the respective case as cut-off in assessment of exposure. The study was approved by the ethical committee: Regional Ethics Committee, Uppsala University; Uppsala, Sweden. DNR 2005:367 and the research was carried out in compliance with the Helsinki Declaration.

Exposure assessment

Use of wireless phones, both mobile and cordless phones, was assessed by a self-administered questionnaire supplemented over the phone. There was no difference regarding supplementary interviews according to being a case (74% supplemented) or a control (70% supplemented). Adjusting for whether or not a supplementary interview was performed did not change the results of the logistic regression analysis. The questionnaire also contained a number of other questions on e.g., occupations, exposure to different agents, smoking habits, medical history including hereditary risk factors, and exposure to ionizing radiation. Also these questions were supplemented over the phone by the interviewer. A structured protocol was used for all questions. Thus, all assessed exposures were included in the questionnaire and if necessary supplemented over the phone at the same time. Results for other exposures will be published separately.

The ear that had mostly been used during calls was assessed by separate questions for mobile and cordless phones; > 50% of the time for one side, or equally much for both sides. After informed consent from the patients medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used for definition of tumour localisation. The matched control was assigned the same side as the tumour of the respective case. The whole procedure was done without knowledge of exposure status. Use of the wireless phone was defined as ipsilateral (≥ 50% of the time), or contralateral (< 50% of the time) in relation to tumour side.

Medical records and reports to the cancer registries were used to categorize histopathology of the tumours. In Table 2 the various diagnoses of benign brain tumours (n = 814) among participating cases are shown. Most were diagnosed with meningioma (n = 709; 87%). As expected there was a female preponderance among the cases.

Table 2 Histopathology of all benign brain tumours

Histopathology	Men		Women		Total	
	n	%	n	%	n	%
Meningioma	200	78.4	509	91.1	709	87.1
Pituitary adenoma	1	0.4	0	0.0	1	0.1
Acoustic neuroma	36	14.1	37	6.6	73	9.0
Hemangioblastoma	11	4.3	6	1.1	17	2.1
Other benign	7	2.7	7	1.3	14	1.7
All benign	255		559		814	

All questionnaires received a unique Id-number that did not disclose if it was a case or a control. Thus, case or control status was not disclosed to the interviewer or during the further data processing. All information was coded and entered into a database. A random sample of questionnaires was coded twice by two independent persons with similar results. Being a case or a control was not disclosed until the statistical analyses.

Statistical methods

All analyses were done using StataSE 12.1 (Stata/SE 12.1 for Windows; StataCorp., College Station TX). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis including the whole control sample (i.e. matched to both malignant and benign cases) to increase the power in the study. This was possible since adjustment/stratification was made for the matching variables (gender, age within 5 years, and year of diagnosis).

The unexposed category consisted of people who reported no use of mobile or cordless phones, or a latency period ≤ 1 year (amount of time between first use of the phone and year of diagnosis). As noted earlier, the same year as for each case's diagnosis was used for the corresponding control as the cut-off for exposure accumulation. Furthermore, because of the low number of unexposed cases, a further criterion was used, i.e. regardless of latency being ≤1 year, cumulative use ≤ 39 hours (3rd percentile) of wireless phones in total among the controls was also used as cut-off for the referent group of "no exposure" among cases and controls. The 3rd percentile was chosen to approximately correspond to one working week.

A latency period ≤ 1 year was used, as in our previous studies, to make it possible to analyse a late effect (promotion) in brain tumour genesis [8,15]. Note that latency was calculated

separately for the respective phone type or combination of phones that were analysed. Latency was analysed using six time periods, >1-5 years, >5-10 years, >10-15 years, >15-20 years, >20-25 years and >25 years. Cumulative use of the phone types was analysed in quartiles based on use of wireless phones in total among the controls (first quartile >39-405 h, second quartile 406–1,091 h, third quartile 1,092-2,376 h, fourth quartile >2,376 h). Latency and cumulative use were also analysed as continuous variables (per year of latency, per 100 h cumulative use) to further explore the dose–response relations.

Adjustment was made for the matching variables gender, age (as a continuous variable), and year of diagnosis. In addition, adjustment was made for socio-economic index (SEI) divided into four categories (blue-collar worker, white-collar worker, self-employed, no work). We had no information if 'no work' indicated unemployment, retirement, living on returns etc. Note that laterality of the tumour was not available for all cases, e.g., for midline tumours, or for tumours in both hemispheres (n = 123). These were dropped from the laterality analysis together with controls matched to cases without laterality data in the whole material (n = 306). Laterality analysis was not made for the whole group of wireless phone users since the side differed for mobile phone and cordless phone for some of the included persons using both phone types (9.8% of the cases, 8.9% of the controls).

Tumour volume was estimated using the ellipsoid formula ($\frac{4}{3}\pi\left(\frac{D_1}{2}\times\frac{D_2}{2}\times\frac{D_3}{2}\right)$; D_1, D_2, D_3 = diameters in the three axis). Change of tumour volume per year of latency and per 100 hours of cumulative use was analysed using linear regression analysis, adjusted for age and gender. The volumes were log-transformed to normalize the distribution. The percentage changes were calculated from the β coefficients in the model, using the expression $\left(e^{\beta-coefficient-1}\right)\times 100$.

In this article results are given for meningioma, whereas the findings for acoustic neuroma will be published separately. The number of other benign brain tumours was too low (n = 32) to make statistical analyses meaningful.

Results

Of the 920 cases with a benign brain tumour 814 (88%) answered the questionnaire, 255 were men and 559 women. For the total sample of 1,601 cases (both malignant and benign brain tumours), an equal number of matched controls received a questionnaire. Note that two cases had two tumours; astrocytoma grade IV and meningioma and ependymoma and acoustic neuroma, respectively. Of these controls, 1,368 (85%) answered the questionnaire, 564 men and 804 women. The mean age was 56 years for cases with benign brain tumour (median 58, range 21–75) and 55 years for all controls (median 58, range 19–75). For meningioma cases the mean age was 57 years (median 59, range 23–75).

In Table 3 the results are shown for meningioma and use of wireless phones. Analogue phones yielded OR = 0.9, 95% CI = 0.6-1.5 and OR = 1.3, 95% CI = 0.6-2.8 in the longest latency group > 25 years.

Table 3 Odds ratio (OR) and 95% confidence interval (CI) for meningioma

Latency	Analogue	Digital (2G)	Digital (UMTS, 3G)	Mobile phone, total	Cordless phone	Digital type[a]	Wireless phone
	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI
	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)
Meningioma (n = 709)							
Total, > 1 y	0.9	1.0	0.7	1.0	1.1	1.0	1.0
	0.6-1.5	0.7-1.4	0.4-1.2	0.7-1.4	0.8-1.5	0.7-1.5	0.7-1.5
	(108/260)	(593/1,208)	(47/140)	(594/1,217)	(522/1,015)	(641/1,261)	(641/1,261)
>1-5 y	-	1.1	0.6	1.1	1.0	1.2	1.2
	(0/0)	0.7-1.7	0.3-1.2	0.7-1.7	0.7-1.5	0.7-1.9	0.7-2.0
		(70/109)	(40/126)	(69/108)	(109/209)	(43/64)	(42/61)
>5-10 y	0.5	0.9	1.1	1.0	1.0	1.0	1.0
	0.1-2.1	0.7-1.4	0.4-3.5	0.7-1.4	0.7-1.5	0.7-1.4	0.7-1.5
	(3/10)	(236/477)	(7/14)	(217/423)	(217/436)	(222/420)	(206/378)
>10-15 y	0.8	1.0	-	1.0	1.1	1.0	1.0
	0.4-1.6	0.7-1.5	(0/0)	0.7-1.4	0.8-1.7	0.7-1.5	0.7-1.5
	(21/51)	(212/453)		(185/399)	(128/248)	(248/523)	(226/466)
>15-20 y	1.1	1.0	-	1.0	1.2	1.1	1.1
	0.6-1.9	0.6-1.5	(0/0)	0.6-1.5	0.7-1.8	0.7-1.6	0.7-1.6
	(39/86)	(75/169)		(78/174)	(61/109)	(121/241)	(115/231)
>20-25 y	0.9	-	-	0.8	1.3	1.2	0.9
	0.5-1.5	(0/0)	(0/0)	0.5-1.4	0.5-3.4	0.5-3.3	0.5-1.5
	(29/80)			(29/80)	(7/13)	(7/13)	(36/92)
>25 y	1.3	-	-	1.2	-	-	1.2
	0.6-2.8	(0/0)	(0/0)	0.6-2.3	(0/0)	(0/0)	0.6-2.4
	(16/33)			(16/33)			(16/33)

Number of exposed cases (Ca) and controls (Co) are given.
Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.
[a]2G, 3G and/or cordless phone.

Use of digital 2G phones yielded in total OR = 1.0, 95% CI = 0.7-1.4. Similar results were found in the different latency group, i.e. no increased risk. Also for digital 3G no statistically significant increased risk was found as well as for mobile phone use in total.

Cordless phone use gave OR = 1.1, 95% CI = 0.8-1.5, with somewhat higher risk in the longest latency group >20-25 years yielding OR = 1.3, 95% CI = 0.5-3.4. Wireless phone use overall gave OR = 1.0, 95% CI = 0.7-1.5 increasing somewhat with latency > 25 years to OR = 1.2, 95% CI = 0.6-2.4. Gender specific analyses did not change the results statistically significant (data not in table).

In Table 4 results are given for use of wireless phones in relation to tumour side. The results were similar for ipsilateral and contralateral use without any statistically significant increased or decreased risk for the different phone types.

Table 4 Odds ratio (OR) and 95% confidence interval (CI) for meningioma, total, ipsilateral and contralateral exposure

	All			Ipsilateral			Contralateral		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue	108/260	0.9	0.6 – 1.5	54/118	1.4	0.8 – 2.4	42/84	1.2	0.6 – 2.2
Digital (2G)	593/1,208	1.0	0.7 – 1.4	283/530	1.1	0.7 – 1.6	214/404	1.1	0.7 – 1.6
Digital (UMTS, 3G)	47/140	0.7	0.4 – 1.2	26/69	0.8	0.4 – 1.8	17/45	0.8	0.3 – 2.1
Mobile phone, total	594/1,217	1.0	0.7 – 1.4	284/534	1.1	0.7 – 1.6	214/407	1.1	0.7 – 1.6
DECT	522/1,015	1.1	0.8 – 1.5	244/454	1.1	0.7 – 1.6	188/327	1.2	0.8 – 1.8

Numbers of exposed cases (Ca) and controls (Co) are displayed.
Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.
Ipsilateral: ≥ 50% use of the phone on the same side as the tumour was located.
Contralateral: < 50% use of the phone on the same side as the tumour was located.

Cumulative use of wireless phones was analysed in quartiles, Table 5. Note that for the various phone types the cumulative time was counted for use of the specific phone, but for the category "mobile phones" all types of mobile phones were included, and for "wireless phones" also use of cordless phones was included. For all studied phone types and combinations highest ORs were found in the fourth quartile with > 2,376 h cumulative use. Mobile phone use gave OR = 1.3, 95% CI = 0.8-1.9 (p trend = 0.34), cordless phone use yielded OR = 1.8, 95% CI = 1.2-2.8 (p trend = 0.0003) and wireless phone use in total gave OR = 1.4, 95% CI = 0.9-2.0 (p trend = 0.01).

Table 5 Odds ratio (OR) and 95% confidence interval (CI) for meningioma for cumulative use of wireless phones in quartiles based on use of wireless phones among controls in total

Quartile	Analogue	Digital (2G)	Digital (UMTS, 3G)	Mobile phone, total	Cordless phone	Digital type	Wireless phone
	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI
	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)
First quartile	0.9	1.0	0.7	1.0	1.0	1.1	1.1
	0.6-1.5	0.7-1.4	0.3-1.3	0.7-1.4	0.7-1.4	0.8-1.6	0.7-1.5
	(77/184)	(317/620)	(30/87)	(306/587)	(194/434)	(185/327)	(178/317)
Second quartile	0.6	1.0	0.4	1.0	0.9	0.9	0.9
	0.3-1.4	0.7-1.5	0.1-1.2	0.7-1.4	0.6-1.3	0.6-1.3	0.6-1.3
	(12/47)	(122/260)	(6/34)	(119/261)	(116/278)	(134/320)	(134/314)
Third quartile	1.3	0.9	0.6	0.9	1.2	0.9	0.9
	0.6-2.9	0.6-1.4	0.2-1.8	0.6-1.4	0.8-1.8	0.6-1.3	0.6-1.4
	(12/23)	(75/199)	(6/17)	(85/210)	(117/194)	(135/317)	(138/315)
Fourth quartile	3.0	1.5	7.3	1.3	1.8	1.4	1.4
	0.9-9.7	0.9-2.3	1.2-46	0.8-1.9	1.2-2.8	0.96-2.0	0.9-2.0
	(7/6)	(79/129)	(5/2)	(84/159)	(95/109)	(187/297)	(191/315)
p, trend	0.11	0.06	0.04	0.34	0.0003	0.002	0.01

Numbers of exposed cases (Ca) and controls (Co) are displayed.
Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.
First quartile >39-405 h; second quartile 406–1091 h; third quartile 1092–2376 h, fourth quartile >2376 h.

OR increased per 100 h cumulative use, statistically significant for all types of phones except for 2G with borderline significance, Table 6. In a multivariate analysis including all phone types (i.e. analogue, 2G, 3G and cordless phone) a statistically significant result was found only for cordless phone (OR = 1.010, 95% CI = 1.005-1.016; data not in table). Wireless phone use increased the risk with OR = 1.006, 95% CI = 1.003-1.009 per 100 h cumulative use. Regarding OR per year of latency no statistically significant increased risk was found. These results did not change if years of use of any mobile or cordless phone prior to the

respective type was included as a covariate in each analysis of the individual phone types (data not in table).

Table 6 Odds ratio (OR) and 95% confidence interval (CI) for meningioma per 100 hours of cumulative use and per year of latency

	Per 100 h cumulative use		Per year of latency	
	OR	95% CI	OR	95% CI
Analogue	1.021	1.0004 – 1.042	1.003	0.982 – 1.025
Digital (2G)	1.005	0.99997 – 1.011	0.999	0.979 – 1.020
Digital (UMTS, 3G)	1.035	1.0002 – 1.071	0.929	0.799 – 1.081
Mobile phone, total	1.005	1.001 – 1.010	0.998	0.982 – 1.014
Cordless phone	1.011	1.006 – 1.017	1.008	0.989 – 1.028
Digital type	1.007	1.003 – 1.010	1.003	0.984 – 1.022
Wireless phone	1.006	1.003 – 1.009	1.000	0.984 – 1.016

Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

In Table 7 results are shown for malignant brain tumours localized in the temporal lobe or overlapping temporal and adjacent lobe. There was no pattern of statistically significant increased risk for any phone type in total or in the different latency groups.

Table 7 Odds ratio (OR) and 95% confidence interval (CI) for meningioma located in temporal (n = 169) and overlapping lobes (temporofrontal (n = 44), temporoparietal (n = 11), temporooccipital (n = 5)); in total n = 229

Latency	Analogue	Digital (2G)	Digital (UMTS, 3G)	Mobile phone, total	Cordless phone	Digital type	Wireless phone
	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI	OR, CI
	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)	(Ca/Co)
Total, > 1 y	1.0	0.8	0.9	0.8	0.9	0.9	0.9
	0.5-1.9	0.5-1.4	0.4-2.1	0.5-1.4	0.5-1.5	0.5-1.5	0.5-1.5
	(35/260)	(188/1,208)	(20/140)	(188/1,217)	(170/1,015)	(205/1,261)	(205/1,261)
>1-5 y	-	0.9	0.9	0.9	0.8	1.1	1.2
	(0/0)	0.5-1.7	0.4-2.2	0.4-1.7	0.5-1.5	0.6-2.3	0.6-2.4
		(21/109)	(19/126)	(21/108)	(33/209)	(16/64)	(16/61)
>5-10 y	-	0.8	0.5	0.8	1.0	0.8	0.8
	(0/10)	0.5-1.3	0.1-5.2	0.4-1.3	0.6-1.6	0.5-1.4	0.5-1.3
		(71/477)	(1/14)	(64/423)	(75/436)	(64/420)	(59/378)
>10-15 y	1.0	0.9	-	0.9	0.9	0.9	0.9
	0.4-2.6	0.5-1.6	(0/0)	0.5-1.5	0.5-1.6	0.6-1.6	0.5-1.5
	(7/51)	(72/453)		(61/399)	(40/248)	(85/523)	(72/466)
>15-20 y	1.1	0.8	-	0.9	0.9	0.9	1.0
	0.4-2.5	0.4-1.6	(0/0)	0.5-1.7	0.5-1.8	0.5-1.6	0.5-1.7
	(12/86)	(24/169)		(26/174)	(19/109)	(37/241)	(39/231)
>20-25 y	1.0	-	-	0.9	1.1	1.2	1.0
	0.4-2.3	(0/0)	(0/0)	0.4-2.0	0.3-4.4	0.3-4.8	0.5-2.0
	(11/80)			(11/80)	(3/13)	(3/13)	(14/92)
>25 y	1.1	-	-	1.0	-	-	1.0
	0.4-3.6	(0/0)	(0/0)	0.4-3.0	(0/0)	(0/0)	0.4-3.0
	(5/33)			(5/33)			(5/33)

Numbers of exposed cases (Ca) and controls (Co) are given.
Adjustment was made for age at diagnosis, gender, SEI-code and year of diagnosis.

The average tumour volume in men was 32.6 cm^3 and 28.7 cm^3 in women ($p = 0.02$). In cases with wireless phone use the average volume was 29.3 cm^3 *versus* 34.9 cm^3 in the unexposed group ($p = 0.11$). Tumour volume did not change statistically significant per year of latency or per 100 hours of cumulative use, see Table 8. We calculated also tumour area and found

no statistically significant association with cumulative use or latency for wireless phone use (data not in table).

Table 8 Percentage change in tumour volume per year of latency and per 100 hours of cumulative use

Type of phone	n	Change in volume per year of latency (%)	95% CI	p	Change in volume per 100 h of cumulative use (%)	95% CI	p
Analogue	98	1.6	−4.7 to 8.3	0.62	0.1	−2.0 to 2.2	0.96
Digital, 2G	530	−0.9	−4.0 to 2.2	0.56	0.1	−0.6 to 0.8	0.83
Digital, UMTS, 3G	41	9.6	−21.1 to 52.4	0.57	1.3	−2.0 to 4.7	0.42
Mobile phone, total	531	−0.5	−2.8 to 1.9	0.68	0.1	−0.5 to 0.6	0.84
DECT	465	−0.8	−3.6 to 2.0	0.57	−0.3	−0.7 to 0.1	0.13
Wireless phone	570	−0.2	−2.5 to 2.1	0.86	−0.2	−0.5 to 0.1	0.19

Adjustment was made for age at diagnosis and gender.

Discussion

The main result of this study was no overall association between use of wireless phones and meningioma. However, somewhat higher OR was found in the longest latency group, > 25 years, for use of analogue phones. A similar result was found for use of cordless phones in the latency group > 20–25 years, the longest time for that phone type. These results were not statistically significant and no statistically significant increased OR was calculated per year of latency.

The highest absorption of RF-EMF emissions from a handheld phone is on the same side of the brain (ipsilateral) as the phone is used, with highest dose in the temporal lobe [9]. In the present study there was no effect of laterality, although somewhat higher OR was calculated for ipsilateral use of an analogue phone than contralateral. No pattern of association was found for meningioma in the temporal and overlapping lobes.

Cumulative use of wireless phones was in our present study divided into quartiles depending on cumulative use of wireless phones in total among controls. For all phone types the highest risk was found in the fourth quartile > 2,376 hours of cumulative use. This corresponds to about 40 min wireless phone use per day for 10 years. There was a statistically significant trend ($p < 0.05$) for increasing cumulative use of 3G mobile phones, cordless phones, phones of the digital type (2G, 3G and/or cordless phone), and wireless phones in total. Especially high OR was calculated for digital 3G phone use, OR = 7.3, 95% CI = 1.2-46, in the fourth quartile, but based on only 5 exposed cases and 2 exposed controls. These results are reflected in Table 6 with a statistically significant increasing risk per 100 h cumulative use for all phone types except for 2G with borderline statistical significance.

Tumour volume was not statistically significant associated with use of wireless phones. However, meningioma grows to a size that depends on the location until symptoms. If pressure of the tumor induces symptoms (e.g. seizures, headache) it might be detected sooner and at a smaller volume than in areas where symptoms might remain unnoticed or not being related to a tumor for a long time. If mobile phone use increases tumor growth rate this might be associated with a larger volume but with earlier diagnosis. To elucidate that possibility to some extent we analysed tumour volume for meningioma located in temporal and adjacent lobes, frontal lobe, and other localisations. No clear trends were found for either of these

locations with respect to change in volume per year of latency and per 100 h of cumulative use (data not in table).

There are some strengths of the study. Cases from the whole Sweden with a benign brain tumour diagnosed during 2007–2009 were included. The prevalence of use of mobile phones was highest in the age group 30–54 years for men and 35–54 years for women for the cases diagnosed during 1997–2003 in our previous study [19]. Thus, we included the age group 18–75 years in this study to allow for a reasonable latency time [23]. This is in contrast to the Interphone study that only included cases aged 30–59 years old.

We included only cases with a histopathological diagnosis of a brain tumour. Hence, we asked the six regional cancer registries not to report cases with only a clinical diagnosis. The reason was that we wanted to get a valid diagnosis of the brain tumour for separate analysis depending on the tumour type. If necessary the histopathological reports were supplemented by records from pathology departments around the country after informed consent from the case. Thus, we were able to make classification of all brain tumours based on WHO codes, see Table 2. It is not probable that exclusion of cases with only clinical diagnosis would have biased the results, since criteria for diagnosis are not expected to be related to habits of wireless phone use.

An advantage of this study was the fairly high response rate among both cases and controls. The response rate was 88% (n = 814) among the finally included cases with benign brain tumour. Of the controls 85% (n = 1,368) answered the questionnaire. These response rates are similar to our previous studies on benign brain tumours, 88% (n = 1,254) among cases and 89% (n = 2,162) among controls [8]. Lower response rates were obtained in the Interphone study especially for controls; meningioma cases 78%, range by centre 56–92%, (n = 2,425), and controls 53%, range 42–74%, (n = 7,658) for controls [16]. To get as valid results as possible it is always necessary to have a high response rate. In fact, not responding controls in Interphone tended to be less frequent users of mobile phone than participating controls leading to underestimation of the risk [24-26].

In the unconditional logistic regression analysis all controls, both to cases with malignant and benign brain tumour, were used so as to maximise the statistical power. This was possible since adjustment was made for the matching variables age, gender, and year of diagnosis. In addition adjustment was made for socioeconomic index since an association between white-collar work and brain tumours has been reported [27]. Analysis using conditional logistic regression yielded overall for wireless phones OR = 1.1, 95% CI = 0.7-1.6 versus OR = 1.0, 95% CI = 0.7-1.5 using unconditional logistic regression (see Table 3). Similar differences were seen for the different phone types i.e. similar estimates using both methods, although with slightly wider confidence intervals in the conditional logistic regression.

One limitation of the study was that it was not possible to obtain an "unexposed" group with enough numbers for meaningful statistical calculations, since practically everybody is using a wireless phone of some kind today. We therefore in addition to latency $\leq$ 1 year used the 3rd percentile (39 h) of cumulative time as cut-off. Another option to obtain more "unexposed" individuals would have been to change the cut-off for latency. However, doing that would limit the possibility to study a late effect (promotion) in brain tumour genesis. Furthermore it is difficult to find users that have been using only one single technology, i.e. NMT, GSM, UMTS etc. Most users have used several technologies and for example regarding 3G phones only one case stated use of only that type of mobile phone and no case or control has used

only analogue phones. Thus, few users hampered statistical analyses of single types of wireless phones.

In our previous studies we have only included living cases so as to get as good assessment of exposure as possible [8,14,28]. Excluding deceased cases might theoretically bias the results, notably if there is no association between use of wireless phones and brain tumour in that patient group or even a protective effect. However, in the present study only 31 cases were deceased so it is unlikely that the results were biased in that respect.

Ionizing radiation is an established risk factor for brain tumours, generally more strongly associated with meningioma than with glioma. Among atomic bomb survivors a greatly increased risk for meningioma has been found, as well as among children with radiation therapy for scalp ringworm [4]. In a review of estimated exposure doses to the brain in eight cohort studies no effect modification on the risk by sex, age at exposure, time since exposure or attained age was observed [5]. In a study on radiation associated tumours following therapeutic cranial radiation there was a positive association between dose of cranial irradiation and development of meningioma with mean latency 21.8 years [29]. Average time interval may be dependent on dose, and interval to tumour appearance of 35, 26 and 19–24 years have been reported for low-, moderate-, and high-dose radiation, respectively [30]. Thus, regarding RF-EMF emissions and an association with meningioma long latency times of decades would be expected. In previous studies results for longest latency times of 10+ years have been displayed.

In our previous study on meningioma [8] diagnostic X-ray of the head and neck was associated with an overall increased risk; OR = 1.9, 95% CI = 1.5-2.4 (to be published). The risk increased to OR = 4.4, 95% CI =2.4-8.2 for $\geq$ 3 times of X-rays using > 1 year latency. However, there was no interaction with mobile phone use (p = 0.52), cordless phone use (p = 0.27), or wireless phone use (p = 0.51). Also in the present study X-ray investigations of the head and neck were assessed. These data are to be further analysed, but based on our previous results it is unlikely that there is an interaction with wireless phone use.

In Interphone statistically significant decreased meningioma risk with OR = 0.79, 95% CI = 0.68-0.91 was reported overall [16]. No effect modification was found for time since start of use. With cumulative call time > 1,640 hours the risk increased somewhat to OR = 1.15, 95% CI = 0.81-1.62. We have discussed the many shortcomings in Interphone elsewhere [19,26].

In the Hardell group study for the time period 1997–2003 somewhat increased risk was found for meningioma in the > 10 year latency group for use of analogue and digital mobile phones and for use of cordless phones. Also ipsilateral use gave somewhat increased risk [8]. Wireless phone in total gave OR = 1.0, 95% CI = 0.9-1.2 increasing to OR = 1.4, 95% CI = 0.97-2.0 in the > 10 years latency group with similar results for both mobile phone and cordless phone [20]. In the present study wireless phone use in total yielded OR = 1.0, 95% CI = 0.7-1.5 with an identical result in the > 10 years latency group (data not in table).

Meta-analysis of use of mobile phones based on the results in Interphone [16] and the Hardell group [8] gave no statistically significant decreased or increased risk [19]. Somewhat increased risk was found for meningioma in the temporal lobe using latency time of $\geq$ 10 years (> 10 years in the Hardell group) with OR = 1.25, 95% CI = 0.31-4.98. Cumulative use $\geq$ 1640 hours yielded OR = 1.35, 95% CI = 0.81-2.23 for ipsilateral use of mobile phone. However, for the most exposed area, temporal lobe, OR = 0.82, 95% CI = 0.31-2.17 was

calculated for ≥ 1,640 hours of cumulative use [19]. Thus, no consistent pattern of an association was found.

Conclusions

No conclusive evidence of an association between use of mobile and cordless phones and meningioma was found in this study. The results are in agreement with previous findings of no consistent evidence of an association between use of mobile and cordless phones and meningioma. The present results strengthen our previous findings of an increased risk for glioma and acoustic neuroma, since a systematic bias in those studies would have been expected also in this study of meningioma using the same methodology. An indication of increased risk for meningioma was seen in the group with highest cumulative use but was not supported by statistically significant increasing risk with latency. However, considering the long latency periods that have been reported for the increased meningioma risk associated with exposure to ionizing radiation it is still too early to make a definitive risk assessment. Results for even longer latency periods of wireless phone use than in this study are desirable.

Consent

Written informed consent was obtained from the subjects for the publication of this report.

Abbreviations

2G, Second generation of mobile phones (GSM); 3G, Third generation of mobile phones (UMTS); 4G, Fourth generation of mobile phones; CI, Confidence interval; CT, Computer tomography; DECT, Desktop cordless phones; GSM, Global System for Mobile Communication; IARC, International Agency for Research on Cancer; MRI, Magnetic resonance imaging; NMT, Nordic Mobile Telephone System; OR, Odds ratio; RF-EMF, Radiofrequency electromagnetic fields; SEI, socio-economic index; UMTS, Universal Mobile Telecommunication System

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MC made the statistical calculations and LH was responsible for drafting of the manuscript. FS and KHM read and gave valuable comments on the manuscript. All authors have read and approved the final version.

Acknowledgements

The study was supported by grants from Cancer- och Allergifonden, Cancerhjälpen, Örebro University Hospital Cancer Fund, Lions, Environmental Health Trust, Pandora-Foundation for Independent Research, Berlin, Germany, and Gigaherz.ch, Schweizerische Interessengemeinschaft Elektrosmog-Betroffener, www.gigaherz.ch. We thank Ms Iréne

Larsson and Mrs Margaretha Sjölund, MSc, for assistance in the data collection and Mr Brian Stein for general support. The reporting of cancer patients from the Oncology Centres in Sweden is acknowledged.

References

1. Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM: **Epidemiology of intracranial meningioma.** *Neurosurgery* 2005, **57:**1088–1095.

2. Cordera S, Bottacchi E, D'Alessandro G, Machado D, De Gonda F, Corso G: **Epidemiology of primary intracranial tumours in NW Italy, a population based study: stable incidence in the last two decades.** *J Neurol* 2002, **249:**281–284.

3. Cea-Soriano L, Wallander MA, García Rodríguez LA: **Epidemiology of meningioma in the United Kingdom.** *Neuroepidemiology* 2012, **39:**27–34.

4. Wiemels J, Wrensch M, Claus EB: **Epidemiology and etiology of meningioma.** *J Neurooncol* 2010, **99:**307–314.

5. Braganza MZ, Kitahara CM, De Berrington González A, Inskip PD, Johnson KJ, Rajaraman P: **Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review.** *Neuro Oncol* 2012, **14:**1316–1324.

6. Korhonen K, Auvinen A, Lyytinen H, Ylikorkala O, Pukkala E: **A nationwide cohort study on the incidence of meningioma in women using postmenopausal hormone therapy in Finland.** *Am J Epidemiol* 2012, **175:**309–314.

7. Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H: **Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression.** *J Neurooncol* 2006, **80:**1–7.

8. Hardell L, Carlberg M, Hansson Mild K: **Pooled analysis of two case–control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997–2003.** *Int J Oncol* 2006, **28:**509–518.

9. Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, Varsier N, Wake K, Wiart J: **Distribution of RF energy emitted by mobile phones in anatomical structures of the brain.** *Phys Med Biol* 2008, **53:**2771–2783.

10. Linde T, Hansson Mild K: **Measurement of low frequency magnetic fields from digital cellular telephones.** *Bioelectromagnetics* 1997, **18:**184–186.

11. Jokela K, Puranen L, Sihvonen AP: **Assessment of the magnetic field exposure due to the battery current of digital mobile phones.** *Health Phys* 2004, **86:**56–66.

12. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L, Straif K: **Carcinogenicity of radiofrequency electromagnetic fields.** *Lancet Oncol* 2011, **12:**624–626.

13. IARC: *Non-Ionizing radiation, Part 2: Radiofrequency Electromagnetic Fields*, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 102. Lyon, France: IARCPress; 2013. Available:http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf [accessed May 23 2013].

14. Hardell L, Carlberg M, Hansson Mild K: **Pooled analysis of two case–control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003.** *Int Arch Occup Environ Health* 2006, **79:**630–639.

15. Hardell L, Carlberg M, Hansson Mild K: **Pooled analysis of case–control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects.** *Int J Oncol*, **38:**1465–1474.

16. Interphone Study Group: **Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study.** *Int J Epidemiol* 2010, **39:**675–694.

17. Hardell L, Carlberg M: **Mobile phones, cordless phones and the risk for brain tumours.** *Int J Oncol* 2009, **35:**5–17.

18. Post- och Telestyrelsen: *Svensk Telemarknad 2010.* Stockholm, Sweden: PTS-ER-2011:15; 2011:24. Available: http://www.statistik.pts.se/pts2011/FILES/RAPPORTER/2010/Telemarknad_2010.pdf [accessed May 21 2013].

19. Hardell L, Carlberg M, Hansson Mild K: **Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma.** *Pathophysiology* 2013, **20:**85–110.

20. Hardell L, Carlberg M, Gee D: *Mobile phone use and brain tumour risk: early warnings, early actions? In Late Lessons from Early Warnings, part 2.* Copenhagen, Denmark: European Environment Agency; 2013:ee. Available: http://www.eea.europa.eu/publications/late-lessons-2/late-lessons-chapters/late-lessons-ii-chapter-21/at_download/file [accessed May 21 2013].

21. Post- och Telestyrelsen: *Svensk Telemarknad första halvåret 2011.* Stockholm, Sweden: PTS-ER-2011:21; 2011:27. Available: http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf [accessed May 21 2013].

22. International Telecommunication Union: *The World in 2011 — ICT Facts and Figures.* Geneva, Switzerland; 2011:2. Available: http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf [accessed May 21 2013].

23. Kundi M: **Essential problems in the interpretation of epidemiologic evidence for an association between mobile phone use and brain tumours.** *C R Physique* 2010, **11:**556–563.

24. 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, Klaeboe L, Kurttio P, Lagorio S, Lönn S, McKinney PA, Montestrucq L, Parslow RC, Richardson L, Sadetzki S, Salminen T, Schüz J, Tynes T, Woodward A: **Validation of short term recall of mobile phone use for the Interphone study.** *Occup Environ Med* 2006, **63:**237–243.

25. Vrijheid M, Deltour I, Krewski D, Sanchez M, Cardis E: **The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk.** *J Expo Sci Environ Epidemiol* 2006, **16:**371–384.

26. Hardell L, Carlberg M, Hansson Mild K: **Methodological aspects of epidemiological studies on the use of mobile phones and their association with brain tumors.** *Open EnvSciences* 2008, **2:**54–61.

27. Preston-Martin S, Mack W: **Neoplasms of the nervous system.** In *Cancer Epidemiology and Prevention.* 2nd edition. Edited by Schottenfeld D, Fraumeni JF Jr. New York: Oxford University Press; 1996:1231–1281.

28. Hardell L, Näsman Å, Påhlson A, Hallquist A, Hansson Mild K: **Use of cellular telephones and the risk for brain tumours: A case–control study.** *Int J Oncol* 1999, **15:**113–116.

29. Chowdhary A, Spence AM, Sales L, Rostomily RC, Rockhill JK, Silbergeld DL: **Radiation associated tumors following therapeutic cranial radiation.** *Surg Neurol Int* 2012, **3:**48. doi:10.4103/2152-7806.96068.

30. Kleinschmidt-DeMasters BK, Lillehei KO: **Radiation-induced meningioma with a 63-year latency period. Case report.** *J Neurosurg* 1995, **82:**487–488.

DOI 10.1515/reveh-2013-0006 — Rev Environ Health 2013; aop

Lennart Hardell* and Michael Carlberg

Using the Hill viewpoints from 1965 for evaluating strengths of evidence of the risk for brain tumors associated with use of mobile and cordless phones[1)]

Abstract

Background: Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. An increased risk of brain tumors is a major concern. The International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect to humans from RF-EMF in May 2011. It was concluded that RF-EMF is a group 2B, i.e., a "possible", human carcinogen. Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 on the association or causation that provides a helpful framework for evaluation of the brain tumor risk from RF-EMF.

Methods: All nine issues on causation according to Hill were evaluated. Regarding wireless phones, only studies with long-term use were included. In addition, laboratory studies and data on the incidence of brain tumors were considered.

Results: The criteria on strength, consistency, specificity, temporality, and biologic gradient for evidence of increased risk for glioma and acoustic neuroma were fulfilled. Additional evidence came from plausibility and analogy based on laboratory studies. Regarding coherence, several studies show increasing incidence of brain tumors, especially in the most exposed area. Support for the experiment came from antioxidants that can alleviate the generation of reactive oxygen species involved in biologic effects, although a direct mechanism for brain tumor carcinogenesis has not been shown. In addition, the finding of no increased risk for brain tumors in subjects using the mobile phone only in a car with an external antenna is supportive evidence. Hill did not consider all the needed nine viewpoints to be essential requirements.

Conclusion: Based on the Hill criteria, glioma and acoustic neuroma should be considered to be caused by RF-EMF emissions from wireless phones and regarded as carcinogenic to humans, classifying it as group 1 according to the IARC classification. Current guidelines for exposure need to be urgently revised.

Keywords: acoustic neuroma; causation; glioma; Hill criteria; wireless phones.

[1)]Based on a presentation at the Corporate Interference with Science and Health: Fracking, Food and Wireless, Scandinavia House, New York City, March 13 and 14, 2013.

***Corresponding author: Lennart Hardell,** MD, PhD, Department of Oncology, University Hospital, SE-701 85 Örebro, Sweden, Phone: +46-19-6021000, Fax: +46-19-101768, E-mail: lennart.hardell@orebroll.se

Michael Carlberg: Department of Oncology, University Hospital, Örebro, Sweden

Background

Mobile phones have been used since the early 1980s, and the Scandinavian countries were among the first in the world to adopt this technology. At first, analog phones [Nordic Mobile Telephone System (NMT)] were used, but in the early 1990s, the digital system [Global System for Mobile Communication (GSM)] was introduced. The analog system was definitely closed down in Sweden on December 31, 2007. Nowadays, mobile phones are used more than landline phones in Sweden (1). Worldwide, estimates of 5.9 billion mobile phone subscriptions were reported at the end of 2011 by the International Telecommunication Union (2).

Desktop cordless telephones have been used in Sweden since the end of the 1980s, first using the analog system, but since the 1990s, the digital variant was used. They are very common both in homes and at workplaces, overtaking telephones connected to landlines.

Wireless phones, i.e., mobile phones and cordless phones, emit radiofrequency electromagnetic fields (RF-EMF) when used. Cordless phones should be given an equal consideration as mobile phones when this type of exposure is assessed. In fact, this has not been the case except for the Hardell group studies in Sweden (3–8). When used, the handheld mobile phones gives exposure

to RF-EMF to the brain, especially to the temporal lobe on the same side where the phone is used, i.e., ipsilateral exposure (9, 10). This has given concern of an increased risk of brain tumors, although other potential health effects from RF-EMF cannot be excluded.

Few studies exist with data on long-term (i.e., >10 years) use of wireless phones and health risks. Regarding brain tumors, only case-control studies from the Hardell group in Sweden (3–8) and the Interphone Study Group (11, 12) give such results. However, Interphone presented results only for mobile phone use. The cases in the Hardell group studies were diagnosed during 1997–2003, whereas Interphone included 16 research centers in 13 countries during varying periods between 2000 and 2004. There was no overlap of included subjects in the Hardell group studies and the Swedish part of Interphone. A Danish cohort study on mobile users (13) has been evaluated to be inconclusive due to serious methodologic problems (14–16).

Because of the widespread use of wireless technology, even a small risk increase would have serious public health consequences. In May 2011, the International Agency for Research on Cancer (IARC) at the World Health Organization (WHO) evaluated the carcinogenic effect of RF-EMF to humans. It included radiation from mobile phones and from other devices that emit similar nonionizing EMFs in the frequency range 30 kHz–300 GHz. It was concluded that RF-EMF is a group 2B, i.e., a "possible", human carcinogen (14, 16).

This conclusion was mainly based on epidemiologic studies from the Hardell group in Sweden and the IARC Interphone study. These studies showed an association between two types of brain tumors, glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones. There was no consistent pattern of an association within the studied latency period (time since first exposure), with the most common benign brain tumor, meningioma, suggesting specificity for these other tumor types.

To further evaluate strengths of evidence, Bradford Hill gave a presidential address at the British Royal Society of Medicine in 1965 that appeared afterward as an article in the *Proceedings of the Royal Society of Medicine* at the height of the tobacco and lung cancer controversy (17). That article on causation provides a helpful framework for assessing the brain tumor risk from wireless phones and offers some very insightful comments that are useful in this context. In the article "The environment and disease: association or causation", Hill offered a list of nine aspects of an association to be considered when deciding if an association is causal. He did not intend to give a list of necessary conditions but warned that he did not believe "that we can usefully lay down some – hard-and-fast rules of evidence that *must* be obeyed before we can accept cause and effect". He wrote, "None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non* (essential requirement)". In fact, temporality (no. 4 in his list) is required for, e.g., infectious diseases; a cause must precede an effect, as noted later (18). However, Hill was correct that in many cases, it is impossible to define the point in time when the disease covertly started. This holds for virtually all chronic diseases and especially for cancer. Meanwhile, an agent may act as a promoter and an existing tumor is stimulated to grow. Tumor promoters are not able to cause a tumor.

Methods

We used the Hill viewpoints to evaluate the causality on brain tumor risk from RF-EMF emitted from wireless phones. The evaluation was based on studies from the Hardell group (3–8) and Interphone (11, 12), the only studies with results on phone use for more than one decade. Other investigations with relevant data on, e.g., laboratory studies, and the incidence of brain tumors were included. More recent comprehensive reviews on this field of research than the IARC evaluation were also considered (8, 19, 20). Furthermore, some data are presented from a new case-control study on brain tumors by the Hardell group, including the time period 2007–2009 (21–23). For statistical methods used to calculate odds ratios (OR) and 95% confidence intervals (CIs), see previous publications from the Hardell group (3–8, 21–23) and Interphone (11, 12). Random-effects model was used for all meta-analyses using StataSE 12.1 (Stata/SE 12.1 for Windows; Stata Corp., College Station, TX, USA). Restricted cubic splines were used to visualize the relationship between latency and cumulative use of wireless phones and the risk of acoustic neuroma and malignant brain tumors, respectively. Adjustment was made for the same variables as in the logistic regression analysis. Four knots were used at the 5th, 35th, 65th, and 95th percentiles.

Results

Strength

The first criterion discussed by Hill is the strength of the association. The highest risk was found for ipsilateral glioma and acoustic neuroma in the highest exposure category based on cumulative use of mobile phones both in Hardell et al. (7, 8) and Interphone (11, 12) (Table 1). Thus, the meta-analysis yielded in total for ipsilateral glioma OR=1.22, 95% CI=0.58–2.55, which increases with cumulative mobile phone use of >1640 h to OR=2.29, 95% CI=1.56–3.37. In addition, regarding acoustic neuroma, the OR was highest for ipsilateral mobile phone use.

Table 1 OR and 95% CI for glioma and acoustic neuroma based on publications from the Hardell group (7, 8) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Ipsilateral						
All	279/374	1.78 (1.40–2.25)	677/753	0.84 (0.69–1.04)	956/1127	1.22 (0.58–2.55)
≥1640 h	29/21	2.94 (1.60–5.41)	100/62	1.96 (1.22–3.16)	129/83	2.29 (1.56–3.37)
Acoustic neuroma						
Ipsilateral						
All	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
≥1640 h	7/21	3.10 (1.21–7.95)	47/46	2.33 (1.23–4.40)	54/67	2.55 (1.50–4.40)

The numbers of exposed cases (Ca) and controls (Co) are given. The use of mobile phones and the risk for glioma and acoustic neuroma are localized on the same side of the brain (ipsilateral) where the mobile phone was mostly used. Results are presented for all use and cumulative use ≥1640 h.

Consistency

Similar results have been found in different studies. As can be seen in Table 2, the results for glioma are similar in Hardell et al. (7) and Interphone (11) when the same inclusion criteria were used. The results by Hardell et al. (4) were recalculated using the same age group, 30–59 years, as in the Interphone study. Cordless phone use was excluded, and such use was included in the "unexposed" group as in the Interphone study. Note that the handheld

Table 2 OR and 95% CI for glioma in the Interphone study (11) compared with the Hardell group (4, 7).

			Hardell group		Interphone	
	20–80 (All)	20–59	30–59	30–59, Cordless among unexposed	30–59	30–59, Appendix 2
Latency ≥10 years						
Ca/Co	88/99	57/74	56/74	56/74	252/232	190/150
OR	2.26	2.15	1.96	1.79	0.98	2.18
95% CI	1.60–3.19	1.41–3.29	1.27–3.01	1.19–2.70	0.76–1.26	1.43–3.31
Latency ≥10 years, ipsilateral						
Ca/Co	57/45	36/30	35/30	35/30	108/82	NR
OR	2.84	2.70	2.48	2.29	1.21	
95% CI	1.82–4.44	1.54–4.73	1.40–4.38	1.33–3.97	0.82–1.80	
Latency ≥10 years, contralateral						
Ca/Co	29/29	20/24	20/24	20/24	49/56	NR
OR	2.18	2.04	1.96	1.71	0.70	
95% CI	1.24–3.85	1.04–4.00	0.995–3.87	0.89–3.28	0.42–1.15	
Cumulative use ≥1640 h						
Ca/Co	42/43	32/37	29/37	29/37	210/154	160/113
OR	2.31	2.23	1.89	1.75	1.40	1.82
95% CI	1.44–3.70	1.30–3.82	1.08–3.30	1.02–3.00	1.03–1.89	1.15–2.89
Cumulative use ≥1640 h, ipsilateral						
Ca/Co	29/21	22/18	20/18	20/18	100/62	NR
OR	2.94	2.71	2.32	2.18	1.96	
95% CI	1.60–5.41	1.36–5.42	1.14–4.73	1.09–4.35	1.22–3.16	
Cumulative use ≥1640 h, contralateral						
Ca/Co	12/12	9/11	8/11	8/11	39/31	NR
OR	2.10	1.99	1.73	1.48	1.25	
95% CI	0.90–4.90	0.77–5.16	0.65–4.63	0.57–3.87	0.64–2.42	

The numbers of cases (Ca) and controls (Co) are given. NR, not reported. Note that >10-year latency were used in the Hardell group studies and contralateral was defined as <50% use of tumor side. Unexposed in the Interphone study (Appendix 2): latency 1–1.9 years; unexposed in Hardell et al.: no use or latency ≤1 year.

cordless phone emits RF-EMF when used, which cannot be neglected (24). The risk would be biased toward unity by including the use of cordless phones in the "unexposed" category. Also excluding the youngest and oldest age groups, as in the Interphone study, may preclude the possibility to find an increased risk (8). The youngest persons may be more sensitive than older ones; in fact, we found the highest risk for glioma and acoustic neuroma in cases with first use of a wireless phone before 20 years old (8). The prevalence of mobile phone use is highest in the age group 30–59 years according to our findings. Excluding older cases diminishes the possibility to find an increased risk, assuming a reasonable latency time. The peak incidence of most brain tumors is at an older age, between 45 and 75 years of age, with median survival of <1 year for glioblastoma (25). In a case series from Canada, all brain tumors showed a bimodal age distribution with one peak in the 0–4 age group and the other in the 60–69 age group (26). It is concluded that, using the same criteria, there is consistency between the Hardell group and Interphone results.

Specificity

The anatomic areas of the brain that absorb the highest wireless phone radiation, e.g., the temporal lobe (9, 10), have the highest risk. Thus, in the latency group ≥10 years, the meta-analyses of Hardell et al. (5, 7) and Interphone (11, 12) gave in total OR=1.48, 95% CI=0.65–3.35, increasing to OR=1.71, 95% CI=1.04–2.26, for glioma in the temporal lobe (Table 3). The meta-analysis gave for acoustic neuroma with latency ≥10 years OR=1.46, 95% CI=0.39–5.47, in total and OR=1.81, 95% CI=0.73–4.45, for ipsilateral use of mobile phones. For ipsilateral acoustic neuroma and cumulative use of mobile phones ≥1640 h, the meta-analysis gave OR=2.55, 95% CI=1.50–4.40 [data not in table, see Hardell et al. (8)]. Regarding acoustic neuroma, reversed causality might be possible. In some of the earlier Interphone studies of the relationship between mobile phone use and acoustic neuroma, there were some indications that because of hearing problems, there is a switching of the ear usually used, thus reducing ipsilateral risk.

Furthermore, there is specificity regarding tumor type. Both the Hardell group and Interphone found increased risk for glioma and acoustic neuroma but not for meningioma in the same sets of studies (3, 4, 11, 12, 21–23).

Temporality

Those with most years since first use have the highest risk, i.e., an effect of time since first use (latency). This is illustrated in Table 4 in studies from the Hardell group. For the study period 2007–2009, OR=1.7, 95% CI=1.04–2.8, was calculated in total for malignant brain tumors, increasing to OR=2.2, 95% CI=1.3–3.8 with latency >20 years (see also Figure 1) (21). The results for acoustic neuroma were based on the study periods 1997–2003 and 2007–2009 (22). Highest risk was calculated in the >20-year-latency group, yielding OR=4.4, 95% CI=2.2–9.0 (see Figure 2). An increased risk with increasing latency may support temporality. It should

Table 3 OR and 95% CI for glioma and acoustic neuroma and mobile phone use in Hardell et al. (5, 7) and Interphone (11, 12).

	Hardell et al.		Interphone		Meta-analysis	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Glioma						
Latency ≥1 year						
All	432/900	1.32 (1.09–1.61)	1666/1894	0.81 (0.70–0.94)	2098/2794	1.03 (0.64–1.66)
Temporal lobe	116/900	1.30 (0.92–1.83)	509/568	0.86 (0.66–1.13)	625/1468	1.04 (0.70–1.56)
Latency ≥10 years						
All	88/99	2.26 (1.60–3.19)	252/232	0.98 (0.76–1.26)	340/331	1.48 (0.65–3.35)
Temporal lobe	28/99	2.26 (1.32–3.86)	94/69	1.36 (0.88–2.11)	122/168	1.71 (1.04–2.81)
Acoustic neuroma						
Latency ≥1 year						
All	130/900	1.66 (1.20–2.28)	643/1308	0.85 (0.69–1.04)	773/2208	1.17 (0.61–2.26)
Ipsilateral	80/374	1.78 (1.23–2.59)	271/471	0.77 (0.59–1.02)	351/845	1.16 (0.51–2.64)
Latency ≥10 years						
All	20/99	2.93 (1.57–5.46)	68/141	0.76 (0.52–1.11)	88/240	1.46 (0.39–5.47)
Ipsilateral	13/45	2.97 (1.42–6.21)	44/52	1.18 (0.69–2.04)	57/97	1.81 (0.73–4.45)

The numbers of cases (Ca) and controls (Co) are given.

Table 4 OR and 95% CI for malignant brain tumors (n=593; 1368 controls) and acoustic neuroma (n=316; 3530 controls): Hardell group studies (21, 22).

Wireless phones	All		>20-Year latency	
	Ca/Co	OR (95% CI)	Ca/Co	OR (95% CI)
Malignant brain tumors	571/1261	1.7 (1.04–2.8)	82/125	2.2 (1.3–3.8)
Acoustic neuroma	227/2472	1.5 (1.1–2.0)	14/126	4.4 (2.2–9.0)

The numbers of cases (Ca) and controls (Co) are given.

be noted that Interphone did find only weak evidence for increased risks with increased latency.

Biologic gradient

There is a clear dose-response effect, i.e., higher cumulative use in hours of wireless phones gives a higher risk with statistically significant trend in the Hardell group studies. In the recent study on malignant brain tumors (21), the highest risk was calculated in the fourth quartile, >2376 h, of mobile phone and cordless phone use (Table 5). This amount of time corresponds to about 40 min of wireless phone use per day for 10 years. For mobile phone use, OR=2.8, 95% CI=1.6–4.8 (p, trend=0.0001), and for cordless phone use, OR=3.1, 95% CI=1.8–5.5 (p, trend <0.0001) were calculated in the forth quartile. Figure 3 illustrates the dose-response effect. Also, for acoustic neuroma, the highest risk was found in the fourth quartile of cumulative use (>1486 h), yielding OR=2.2, 95% CI=1.5–3.4 in total (p, trend=0.03) [see Hardell et al. (22) and Figure 4].

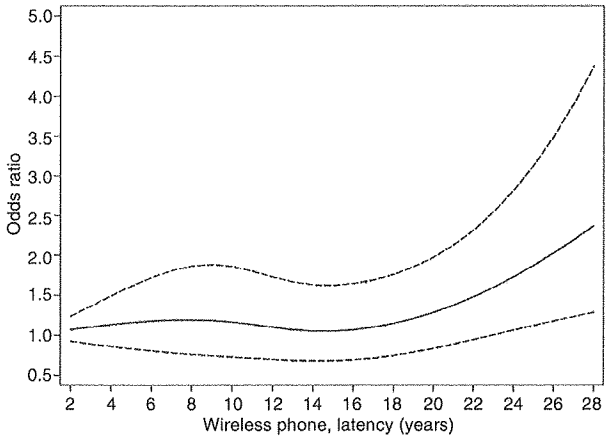


Figure 1 Restricted cubic spline plot of the relationship between latency of wireless phone use and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

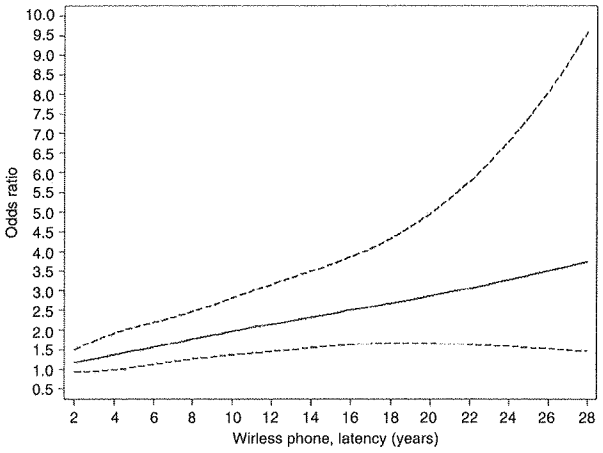


Figure 2 Restricted cubic spline plot of the relationship between latency of wireless phone use and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

In contrast, Interphone, although reporting a significant OR for the highest decile of hours of use, did not find a dose-response relationship for glioma (11). However, it should be noted that according to Appendix 2, with few exceptions, all ORs were >1.0 for glioma in contrast to meningioma. The highest ORs for glioma were found in one of the two highest exposure categories for time since the start of regular use, cumulative call time, and cumulative number of calls. The greatest increase was with increasing time since the start of use of mobile phone. A risk of brain tumors in relation to estimated RF dose from mobile phones in joules per kilogram was reported from five Interphone countries (27). A dose-response relationship for exposure 7+ years ago was reported.

Plausibility

An increase in both single- and/or double-strand breaks of DNA has been detected in humans (28), animal models (29–31), and cell cultures (32, 33). RF-EMF may stimulate reactive oxygen species (ROS) generation both in vivo (34) and in vitro (35). The formation of ROS is considered to be one of the primary mechanisms that are involved in the bio-effects that are mediated by RF-EMF exposure (36).

In a study using a mouse spermatocyte-derived cell line, it was demonstrated that RF-EMF exposure can

Table 5 OR and 95% CI for malignant brain tumors (n=593, 1368 controls) based on Hardell et al. (21).

Quartile	Mobile phone, total			Cordless phone			Wireless phone		
	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co
First quartile	1.4	0.8–2.3	190/587	1.3	0.8–2.2	164/434	1.5	0.9–2.5	108/317
Second quartile	1.7	1.02–3.0	126/261	1.7	1.01–3.0	120/278	1.4	0.8–2.4	110/314
Third quartile	1.5	0.9–2.7	95/210	2.1	1.2–3.7	98/194	1.7	1.003–2.9	137/315
Fourth quartile	2.8	1.6–4.8	137/159	3.1	1.8–5.5	79/109	2.5	1.5–4.2	216/315
p, Trend	0.0001			<0.0001			0.0001		

The numbers of exposed cases (Ca) and controls (Co) are given. First quartile, >39–405 h; second quartile, 406–1091 h; third quartile, 1092–2376 h; fourth quartile, >2376 h according to cumulative use among controls.

increase ROS production and subsequently induce the formation of oxidative base damage as evaluated by FPG-comet assay and 8-oxoG formation (37). To further elucidate the central role of ROS in RF-EMF exposure-induced DNA base damage, the authors used α-tocopherol pretreatment to antagonize the oxidation of ROS; α-tocopherol is an important lipophilic antioxidant that can inactivate harmful ROS. The protective role of α-tocopherol pretreatment confirmed that ROS are involved in RF exposure-induced DNA base damage (37).

However, these studies do not provide a biologic mechanism behind the influence of RF-EMF on brain tumors. Hill pointed out that biologic plausibility cannot be demanded because of the dependency on the limited knowledge of the day. Causality would be strongly supported if rather specific mutations should be demonstrated. Unfortunately, there are currently no studies that address this issue.

Coherence

Brain and nervous system cancer rates, potential confounders, and environmental risk factors were studied in 165 of 208 countries using ecologic data (38). The only exogenous risk factor consistently associated with higher incidence was the penetration of rate of mobile/cellular telecommunication subscriptions. According to these ecologic results, the latency period is at least 11–12 years but probably more than 20 years.

The incidence of brain tumor has been studied in different countries. An increasing incidence of brain tumors, especially of the type that would be expected based on epidemiologic results (glioblastoma multiforme), in the most exposed parts of the brain (temporal and adjacent lobes) has been shown. Such studies are listed below and are more discussed elsewhere (8).

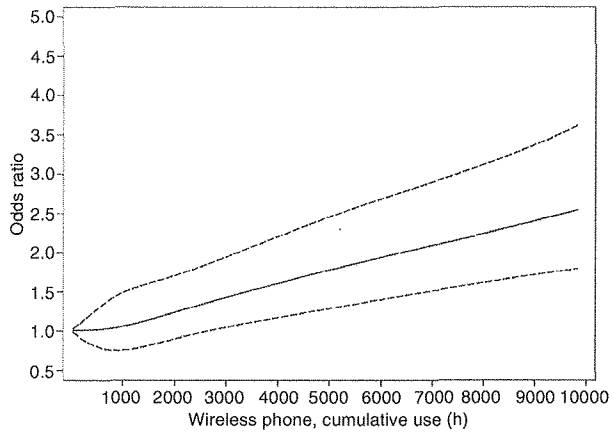


Figure 3 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and malignant brain tumors (21). The solid line indicates the OR estimate, and the broken lines represents the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

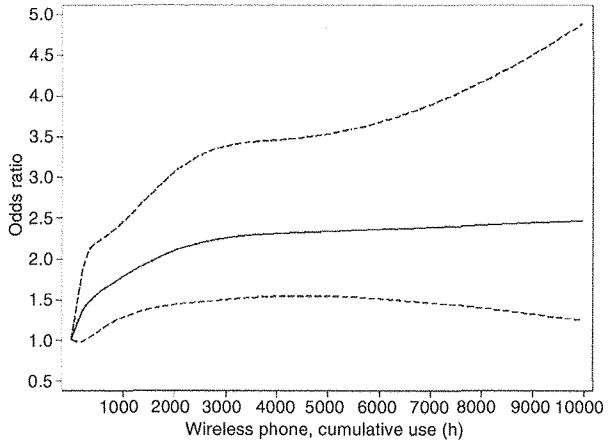


Figure 4 Restricted cubic spline plot of the relationship between cumulative use of wireless phones and acoustic neuroma (22). The solid line indicates the OR estimate, and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI code (four categories: blue-collar worker, white-collar worker, self-employed, and no work), and year of diagnosis.

- United States: High-grade glioma (1992–2008): SEER annual percentage change (APC), +0.64%, 95% CI=+0.33 to +0.95% (39) Microscopically confirmed glioblastoma multiforme (1992–2006): SEER APC, +2.4% to +3.0% ($p \leq 0.001$) (frontal lobe), +1.3% to +2.3% ($p \leq 0.027$) (temporal lobe), across all registries (40). In the parietal and occipital lobes or in overlapping lobes, no statistically significant changes in incidence were seen.
- England: Brain tumors (majority, glioma; 1998–2007): increasing incidence in the temporal lobe for men and women ($p<0.01$) (41) Malignant brain tumors (1998–2011): the age-standardized incidence rates for frontal and temporal lobe tumors in England rose at an average annual percentage change (AAPC) of +3.7%, 95% CI=+2.9% to +4.6% ($p<0.0001$). The overall rates for all (C71) malignant tumors increased slightly. The results show that the pattern of change in incidence over time is statistically significant different for frontal and temporal lobe tumors compared with all other brain tumors (Alasdair Philips, Powerwatch, UK, personal communication, to be published).
- Australia: Malignant brain tumors (2000–2008): APC, +3.9%, 95% CI=+2.4% to +5.4% (42)
- Denmark: Brain and central nervous system tumors (2000–2009): men: APC, +2.7%, 95% CI=+1.1% to +4.3%; women: APC, +2.9%, 95% CI=+0.7% to +5.2% (15)
- Sweden: Astrocytoma (glioma; 2000–2007): age group >19 years: APC, +2.16%, 95% CI=+0.25% to +4.10% (5)

Experiment

The RF-EMF toxic effects on DNA mediated by ROS can be prevented by antioxidants, as shown in several studies. Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (43, 44). The protective role of α-tocopherol pretreatment in RF exposure-induced DNA base damage was recently demonstrated by Liu et al. (37). However, there is no direct relationship between these findings and brain tumor development because no useful animal model has been investigated so far that shows an increased brain tumor incidence after RF-EMF exposure that could be inhibited by antioxidants.

No studies exist on the risk for brain tumors among subjects that have used a wireless phone previously but are current nonusers. However, especially in the 1980s, mobile phone use was common in cars, with a fixed external antenna as the only mode of use. Such use has been assessed in the Hardell group studies and considered to be no exposure to RF-EMF. For the study period 1 January 1997–30 June 2000, among 1429 responding cases and 1470 controls, 73 cases and 90 controls had always used the mobile phone with fixed external antenna and 1 additional control had always used a hands-free device (45). This yielded crude OR=0.8, 95% CI=0.6–1.1. Thus, this "experiment" showed that if the RF-EMF exposure from the mobile phone was protected, no increased risk was found.

Analogy

Animal carcinogenicity of RF-EMF was evaluated by the IARC Working Group in May 2011 (14, 16). There was limited evidence of carcinogenicity in experimental animals. Four classes of cancer bioassays in animals were reviewed. Although an increased cancer risk was found in some studies, it was concluded that there was no consistent pattern of increased risk in seven 2-year cancer bioassays, 12 studies that used different tumor-prone animal models and 16 studies of promotion and initiation. Of six co-carcinogenesis studies involving five different animal models, four responses were reported (16). It should be mentioned that, for example, increased risk (initiation) or earlier development (promotion) of total cancer including malignant lymphoma (46), mammary tumors (47), skin cancer (48), and lymphoma (49) has been reported from RF-EMF exposure.

Discussion

Bradford Hill warned against the misuse of tests of statistical significance. He noted, "We must not be too ready to dismiss a cause-and-effect hypothesis merely on the ground that the observed association appears to be slight". As noted by Kundi (50), the nine issues discussed by Hill were not intended to dismiss a factor as potentially causing a disease. However, the Hill criteria were used in an overall assessment of mobile phone use and brain cancer and other tumors by Repacholi et al. (51). The authors concluded, "In summary, none of the Hill criteria support a causal relationship between wireless phone use and brain cancer or other tumors in the areas of the head that most absorb the RF energy from wireless phones". This conclusion goes far beyond what the authors studied using less reliable methods. For example, they claimed that the use of "wireless phones" was assessed, although only mobile phones were considered and not cordless desktop phones. There are several other reasons to regard this article as less

informative. For example, the Interphone study on acoustic neuroma (12) was not included, although it was available at that time, with partly the same authors. In addition, the article by Cardis et al. (27) on risk of brain tumors in relation to estimated RF dose from mobile phones was omitted despite being available on line (27). Furthermore, no analyses were performed on ipsilateral or contralateral mobile phone use. The authors used the Interphone exposure criteria for effect estimates without considering our definition that was readily available in our publications and also discussed in detail elsewhere (7, 52). The Danish cohort study on mobile phone subscribers (13) was included, although several methodologic shortcomings including the lack of individual exposure data were inherent (15).

Regarding the strength of evidence, there is clearly an increased risk for glioma and acoustic neuroma in the highest exposure category of cumulative use of mobile phones both in the Hardell group studies and Interphone.

Consistency can only be answered by a repetition of the circumstances and observations both by the same research group and other investigators. According to Table 2 and the IARC evaluation (14, 16), the results of increased risk regarding mobile phone use and risk of glioma and acoustic neuroma are similar in the Hardell group and Interphone studies. Unfortunately, Interphone has not published data on cordless phone use, although the Hardell group has published similar results as for mobile phones. Hill also gives an interesting remark that is an answer to those scientists who insist that every positive study must be replicated, "Once again looking at the obverse of the coin there will be occasions when repetition is absent or impossible and yet we should not hesitate to draw conclusions". However, in this case, results have been repeated and we are beyond that comment.

Hill writes, "if *specificity* exists we may be able to draw conclusions without hesitation". Table 3 presents increased risk for glioma in the temporal lobe with highest risk in the ≥10-year latency group. For acoustic neuroma, the ipsilateral use of the mobile phone gives the highest risk. Moreover, the increased risk is specific for glioma and acoustic neuroma, whereas no increased risk was found for meningioma in the same studies (3, 8, 11, 23).

The fourth issue discussed by Hill deals with temporality. As exemplified in Table 4 and Figures 1 and 2, the risk increases with latency with highest OR for both malignant brain tumors and acoustic neuroma in the >20-year-latency group. This is by far the longest latency (time from first use to diagnosis) that has been published.

With a biologic gradient or a dose-response curve, "then we should look most carefully for such evidence". Clearly, in Table 5, a statistically significant biologic gradient is demonstrated for malignant brain tumors and the use of both mobile phones and cordless phones. This is visualized for wireless phone use in Figures 3 and 4.

Regarding plausability, Hill states to those who insist that we wait until the exact causal mechanism is established: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day". To those who insist on more in vivo or in vitro evidence, he states: "Nevertheless, while such laboratory evidence can enormously strengthen the hypothesis and, indeed, may determine the actual causative agents, the lack of such evidence cannot nullify the epidemiological observations in man". Regarding plausibility, as reviewed, oxidative stress is one important mechanism for adverse health effects from RF-EMF emissions. However, it should be pointed out that the exact mechanism for RF-EMF initiation of brain tumors has not been identified.

Bradford Hill discusses coherence among cigarette smoking, lung cancer, and the temporal rise in the two variables over the last generation. No doubt, there are now studies that show an increasing incidence of brain tumors. However, considering the long latency periods of decades in brain tumor genesis, it is currently too early to predict the real incidence increase. By now, there are also studies that show different patterns of incidence for malignant brain tumors in the frontal and temporal lobes compared with the other lobes. This highlights the need of improved data quality in the cancer registries on anatomic localization of the tumors.

Experiment with prevention is one option, especially in industry. Exposure to vinyl chloride and the increased risk of angiosarcoma in the liver is one example of prevention that gave a reduced number of victims (53). Antioxidants like melatonin and vitamins C and E can alleviate the ROS oxidation and apoptosis that are induced by RF-EMF in an animal model (37, 43, 44). No risk increase for brain tumors was found in subjects using external antenna in a car during mobile phone calls without any other wireless phone use (45).

As to the ninth point, analogy, Hill wrote, "In some circumstances it would be fair to judge by analogy". Although he does not discuss this in depth, animal studies may be useful. As stated by IARC, the evidence is limited in experimental animals for carcinogenesis.

Hill noted that, "However, before deducing 'causation' and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.... If we are wrong in

deducing causation from associations no great harm will be done... All scientific work is incomplete... That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time". These wise rules should also be considered when RF-EMF from wireless phones is evaluated as a human carcinogen.

Conclusions

Based on Hill's viewpoints and his discussion on how these issues should be used, the conclusion of this review is that glioma and acoustic neuroma are caused by RF-EMF emissions from wireless phones. According to the IARC Preamble (54), the classification should be group 1, i.e., "the agent is carcinogenic to humans", and urgent revision of current guidelines for exposure is needed.

Acknowledgments: This work was supported by grants from Cancer-och Allergifonden, Cancerhjälpen, Pandora-Foundation for Independent Research, Berlin, Germany, and Gigaherz.ch, Schweizerische Interessengemeinschaft Elektrosmog-Betroffener, www.gigaherz.ch.

Received May 31, 2013; accepted September 13, 2013

References

1. Post-och Telestyrelsen. Svensk Telemarknad första halvåret 2011. Available at: http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf. Accessed on May 31, 2013.
2. International Telecommunication Union. The world in 2011 – ICT facts and figures. Available at: http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf. Accessed on May 31, 2013.
3. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on the use of cellular and cordless telephones and the risk of benign brain tumours diagnosed during 1997–2003. Int J Oncol 2006;28:509–18.
4. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of two case-control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003. Int Arch Occup Environ Health 2006;79:630–9.
5. Hardell L, Carlberg M. Mobile phones, cordless phones and the risk for brain tumours. Int J Oncol 2009;35:5–17.
6. Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. Int J Oncol 2011;38:1465–74.
7. Hardell L, Carlberg M, Hansson Mild K. Re-analysis of risk for glioma in relation to mobile telephone use: comparison with the results of the Interphone international case-control study. Int J Epidemiol 2011;40:1126–8.
8. Hardell L, Carlberg M, Hansson Mild K. Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma. Pathophysiology 2013;20:85–110.
9. Cardis E, Deltour I, Mann S, Moissonnier M, Taki M, et al. Distribution of RF energy emitted by mobile phones in anatomical structures of the brain. Phys Med Biol 2008;53:2771–83.
10. Gandhi OP, Morgan LL, de Salles AA, Han YY, Herberman RB, et al. Exposure limits: the underestimation of absorbed cell phone radiation, especially in children. Electromagn Biol Med 2012;31:34–51.
11. Interphone Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol 2010;39:675–94.
12. Interphone Study Group. Acoustic neuroma risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Cancer Epidemiol 2011;35:453–64.
13. Schüz J, Jacobsen R, Olsen JH, Boice JD Jr, McLaughlin JK, et al. Cellular telephone use and cancer risk: update of a nationwide Danish cohort. J Natl Cancer Inst 2006;98:1707–13.
14. Baan R, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of radiofrequency electromagnetic fields. Lancet Oncol 2011;12:624–6.
15. Söderqvist F, Carlberg M, Hardell L. Review of four publications on the Danish cohort study on mobile phone subscribers and risk of brain tumours. Rev Environ Health 2012;27:51–8.
16. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Non-ionizing radiation, Part 2: radiofrequency electromagnetic fields. Volume 102. Available at: http://monographs.iarc.fr/ENG/Monographs/vol102/mono102.pdf. Accessed on May 31, 2013.
17. Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
18. Rothman KJ. Causation and causal inference. In: Schottenfeld D, Fraumeni JF, editors. Cancer epidemiology and prevention. Philadelphia: WB Saunders, 1982:15–22.
19. Hardell L, Carlberg M, Gee D. Mobile phone use and brain tumour risk: early warnings, early actions? In: Late lessons from early warnings, part 2. Copenhagen, Denmark: European Environment Agency, 2013. Available at: http://www.eea.europa.eu/publications/late-lessons-2/late-lessons-chapters/late-lessons-ii-chapter-21/at_download/file. Accessed on May 31, 2013.
20. BioInitiative Working Group. The BioInitiative Report 2012. A rationale for biologically-based public exposure standards for electromagnetic fields (ELF and RF). Available at: http://www.bioinitiative.org. Accessed on May 31, 2013.

21. Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Case-control study of the association between malignant brain tumors diagnosed 2007–2009 and mobile and cordless phone use. Int J Oncol 2013 [in press].
22. Hardell L, Carlberg M, Söderqvist F, Hansson Mild K. Pooled analysis of case-control studies on acoustic neuroma diagnosed 1997–2003 and 2007–2009 and use of mobile and cordless phones. Int J Oncol 2013;43:1036–44.
23. Carlberg M, Söderqvist F, Hansson Mild K, Hardell L. Meningioma patients diagnosed 2007–2009 and the association with use of mobile and cordless phones. Environ Health 2013;12:60.
24. Redmayne M, Inyang I, Dimitriadis C, Benke G, Abramson MJ. Cordless telephone use: implications for mobile phone research. J Environ Monit 2010;12:809–12.
25. Ohgaki H, Kleihues P. Population-based studies on incidence, survival rates, and genetic alterations in astocytic and oligodendroglial gliomas. J Neuropathol Exp Neurol 2005;64:479–89.
26. Sutherland GR, Florell R, Louw D, Choi NW, Sima AA. Epidemiology of primary intracranial neoplasms in Manitoba, Canada. Can J Neurol Sci 1987;14:586–92.
27. Cardis E, Armstrong BK, Bowman JD, Giles GG, Hours M, et al. Risk of brain tumours in relation to estimated RF dose for mobile phones: results from five Interphone countries. Occup Environ Med 2011;68:631–40.
28. Yadav AS, Sharma MK. Increased frequency of micronucleated exfoliated cells among humans exposed in vivo to mobile telephone radiations. Mutat Res 2008;650:175–80.
29. Lai H, Singh NP. Acute low-intensity microwave exposure increases DNA single-strand breaks in rat brain cells. Bioelectromagnetics 1995;16:207–10.
30. Lai H, Singh NP. Single- and double-strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. Int J Radiat Biol 1996;69:513–21.
31. Kesari KK, Behari J, Kumar S. Mutagenic response of 2.45 GHz radiation exposure on rat brain. Int J Radiat Biol 2010;86:334–43.
32. Diem E, Schwarz C, Adlkofer F, Jahn O, Rüdiger H. Non-thermal DNA breakage by mobile-phone radiation (1800 MHz) in human fibroblasts and in transformed GFSH-R17 rat granulosa cells in vitro. Mutat Res 2005;583:178–83.
33. Paulraj R, Behari J. Single strand DNA breaks in rat brain cells exposed to microwave radiation. Mutat Res 2006;596:76–80.
34. Avci B, Akar A, Bilgici B, Tunçel ÖK. Oxidative stress induced by 1.8 GHz radio frequency electromagnetic radiation and effects of garlic extract in rats. Int J Radiat Biol 2012;88:799–805.
35. Lu YS, Huang BT, Huang YX. Reactive oxygen species formation and apoptosis in human peripheral blood mononuclear cell induced by 900 MHz mobile phone radiation. Oxid Med Cell Longev 2012;2012:740280.
36. Friedman J, Kraus S, Hauptman Y, Schiff Y, Seger R. Mechanism of short-term ERK activation by electromagnetic fields at mobile phone frequencies. Biochem J 2007;405:559–68.
37. Liu C, Duan W, Xu S, Chen C, He M, et al. Exposure to 1800 MHz radiofrequency electromagnetic radiation induces oxidative DNA base damage in a mouse spermatocyte-derived cell line. Toxicol Lett 2013;218:2–9.
38. de Vocht F, Hannam K, Buchan I. Environmental risk factors for cancers of the brain and nervous system: the use of ecological data to generate hypotheses. Occup Environ Med 2013;70:349–56.
39. Little MP, Rajaraman P, Curtis RE, Devesa SS, Inskip PD, et al. Mobile phone use and glioma risk: comparison of epidemiological study results with incidence trends in the United States. BMJ 2012;344:e1147.
40. Zada G, Bond AE, Wang YP, Giannotta SL, Deapen D. Incidence trends in the anatomic location of primary malignant brain tumors in the United States: 1992–2006. World Neurosurg 2012;77:518–24.
41. de Vocht F, Burstyn I, Cherrie JW. Time trends (1998–2007) in brain cancer incidence rates in relation to mobile phone use in England. Bioelectromagnetics 2011;32:334–9.
42. Dobes M, Shadbolt B, Khurana VG, Jain S, Smith SF, et al. A multicenter study of primary brain tumor incidence in Australia (2000–2008). Neuro Oncol 2011;13:783–90.
43. Oral B, Guney M, Ozguner F, Karahan N, Mungan T, et al. Endometrial apoptosis induced by a 900-MHz mobile phone: preventive effects of vitamins E and C. Adv Ther 2006;23:957–73.
44. Ozguner F, Bardak Y, Comlekci S. Protective effects of melatonin and caffeic acid phenethyl ester against retinal oxidative stress in long-term use of mobile phone: a comparative study. Mol Cell Biochem 2006;282:83–8.
45. Hardell L, Hallquist A, Hansson Mild K, Carlberg M, Påhlson A, et al. Cellular and cordless telephones and the risk for brain tumours. Eur J Cancer Prev 2002;11:377–86.
46. Chou CK, Guy AW, Kunz LL, Johnson RB, Crowley JJ, et al. Long-term, low-level microwave irradiation of rats. Bioelectromagnetics 1992;13:469–96.
47. Frei MR, Jauchem JR, Dusch SJ, Merritt JH, Berger RE, et al. Chronic, low-level (1.0 W/kg) exposure of mice prone to mammary cancer to 2450 MHz microwaves. Radiat Res 1998;150:568–76.
48. Szmigielski S, Szudzinski A, Pietraszek A, Bielec M, Janiak M, et al. Accelerated development of spontaneous and benzopyrene-induced skin cancer in mice exposed to 2450-MHz microwave radiation. Bioelectromagnetics 1982;3:179–91.
49. Repacholi MH, Basten A, Gebski V, Noonan D, Finnie J, et al. Lymphomas in E mu-Pim1 transgenic mice exposed to pulsed 900 MHZ electromagnetic fields. Radiat Res 1997;147:631–40.
50. Kundi M. Causality and the interpretation of epidemiologic evidence. Environ Health Perspect 2006;114:969–74.
51. Repacholi MH, Lerchl A, Röösli M, Sienkiewicz Z, Auvinen A, et al. Systematic review of wireless phone use and brain cancer and other head tumors. Bioelectromagnetics 2012;33:187–206.
52. Hardell L, Carlberg M, Hansson Mild K. Methodological aspects of epidemiological studies on the use of mobile phones and their association with brain tumors. Open Environ Sci 2008;2:54–61.
53. Holmberg B. The toxicology of monomers of the polyvinyl plastic series. Prog Clin Biol Res 1984;141:99–112.
54. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Preamble. Lyon, France: WHO, IARC, 2006.

EXHIBIT E

FCC 13-39

Before the Federal Communications Commission

Washington, D.C. 20554

In the Matter of

Reassessment of Federal Communications Commission Radiofrequency Exposure Limits and Policies	)	ET Docket No. 13-84
Proposed Changes in the Commission's Rules Regarding Human Exposure to Radiofrequency Electromagnetic Fields	)	ET Docket No. 03-137

To: Office of the Secretary
Federal Communications Commission , Washington, DC 20554

As officially presented in the Federal Register/ Vol. 78, No. 107 / Tuesday, June 4, 2013 / Proposed Rules. Federal Communications Commission, 47 CFR Parts 1, 2, 15, 24, 25, 27, 73, 90, 95, 97, and 101 [ET Docket Nos. 03–137 and 13–84; FCC 13–39], Reassessment of Exposure to Radiofrequency Electromagnetic Fields Limits and Policies, Federal Communications Commission

Comment Filed by: Cindy Sage, Sage Associates
1396 Danielson Road, Santa Barbara, CA 93108
E-mail: sage@silcom.com Tel.: 805-969-0557

Prof. Lennart Hardell, MD, PhD
Department of Oncology Orebro University Hospital Orebro, Sweden
E-mail: lennart.hardell@orebroll.se

Dr. Martha Herbert, PhD, MD, Pediatric Neurology
TRANSCEND Research Program Massachusetts General Hospital
Harvard Medical School Boston, MA USA
Email: drmarthaherbert@gmail.com

1. New, biologically-based public exposure standards should be developed under the direction of experts in the biological effects and adverse health effects of chronic exposures to radiofrequency electromagnetic radiation (RFR), drawing upon the substantial international body of scientific and public health literature, and not be limited to individuals in electrical and electronic engineering.

2. A rapidly accumulating body of scientific evidence of harm to health and well-being constitute warnings that adverse health effects can occur with prolonged exposures to very low-intensity EMF at biologically active frequencies or frequency combinations.

3. The BioInitiative 2012 Report reports biological effects at exposure levels significantly below the 2007 recommended goal of 0.1 uW/cm2. Since 2007, five new studies of base-station level RFR at intensitites ranging from less than 0.001 uW/cm2 to 0.05 uW/cm2 report headaches, concentration difficulties and behavioral problems in children and adolescents; and sleep disturbances, headaches and concentration problems in adults. Exhibit A presents some representative studies (peer-reviewed and published in reputable scientific journals) that report biological effects and adverse health effects at levels that are clearly non-thermal (low-intensity). New biologically-based public exposure limits are critically needed in light of the vast rollout of wireless technologies that expose billions of people globally to elevated, artificial RFR (particularly pulsed RFR) in daily life. These studies are representative of several thousand studies over four decades that constitute emerging scientific evidence of risk to very low-intensity RFR with chronic exposure.

4. As new studies are completed and published on the effects of chronic, low-intensity RFR exposure across populations (from cell towers and wireless devices, for example) the results indicate adverse health impacts occur from on-going disruption of normal metabolism, endocrine function, male fertility parameters, fetal brain development, immune function, mental abilities, electrophysiology, and neural synchrony. Disruption of basic neural function due to artificial EMF/RFR exposures can disrupt weak-field effects that are necessary to guide non-linear biological oscillations and other cellular communications necessary for normal biological functioning, and result in unacceptable burdens on human health.

5. Evidence for Damage to Sperm and Reproduction

Evidence for damage to sperm and male reproduction parameters include adverse effects on sperm quality, motility and pathology in men who use and particularly those who wear a cell phone, PDA or pager on their belt or in a pocket (Agarwal et al, 2008; Agarwal et al, 2009; Wdowiak et al, 2007; De Iuliis et al, 2009; Fejes et al, 2005; Aitken et al, 2005; Kumar, 2012). Other studies conclude that usage of cell phones, exposure to cell phone radiation, or storage of a mobile phone close to the testes of human males affect sperm counts, motility, viability and structure (Aitken et al, 2004; Agarwal et al, 2007; Erogul et al, 2006). Animal studies have demonstrated oxidative and DNA damage, pathological changes in the testes of animals, decreased sperm mobility and viability, and other measures of deleterious damage to the male germ line (Dasdag et al, 1999; Yan et al, 2007; Otitoloju et al, 2010; Salama et al, 2008; Behari et al, 2006; Kumar et al, 2012). There are fewer animal studies that have studied effects of cell phone radiation on female fertility parameters. Panagopoulous et al (2012) report decreased ovarian development and size of ovaries, and premature cell death of ovarian follicles and nurse cells in *Drosophila melanogaster*. Gul et al (2009) reported rats exposed to stand-by level RFR (phones on but not transmitting calls) had a decrease in the number of ovarian follicles in pups born to these exposed dams. Magras and Xenos (1997) reported irreversible infertility in mice after five (5) generations of exposure to RFR at cell phone tower exposure levels of less than one

microwatt per centimeter squared (μW/cm2). See www.bioinitiative.org Section 18 for references.

HUMAN SPERM AND THEIR DNA ARE DAMAGED

Human sperm are damaged by cell phone radiation at very low intensities (0.00034 – 0.07 μW/cm2). Many new studies in the last decade report sperm damage in humans and animals, leading to substantial concerns for fertility, reproduction and health of the offspring (unrepaired de novo mutations in sperm). Exposure levels are similar to those resulting from wearing a cell phone on the belt, or in the pants pocket, or using a wireless laptop computer on the lap. Sperm lack the ability to repair DNA damage.

6. Evidence for Brain Tumors

Based on epidemiological studies there is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The evidence comes mainly from two study centres, the Hardell group in Sweden and the Interphone Study Group. No consistent pattern of an increased risk is seen for meningioma. A systematic bias in the studies that explains the results would also have been the case for meningioma. The different risk pattern for tumor type strengthens the findings regarding glioma and acoustic neuroma. Meta-analyses of the Hardell group and Interphone studies show an increased risk for glioma and acoustic neuroma. Supportive evidence comes also from anatomical localisation of the tumor to the most exposed area of the brain, cumulative exposure in hours and latency time that all add to the biological relevance of an increased risk. In addition risk calculations based on estimated absorbed dose give strength to the findings. See www.bioinitiative.org Section 11 for references.

- There is reasonable basis to conclude that RF-EMFs are bioactive and have a potential to cause health impacts.
- There is a consistent pattern of increased risk for glioma and acoustic neuroma associated with use of wireless phones (mobile phones and cordless phones) mainly based on results from case-control studies from the Hardell group and Interphone Final Study results.
- Epidemiological evidence gives that RF-EMF should be classified as a human carcinogen.
- The existing FCC/IEE and ICNIRP public safety limits and reference levels are not adequate to protect public health based on evidence for brain tumors and RFR exposure.
- New public health standards and limits are needed.

7. Evidence for Adverse Fetal and Neonatal Effects

Effects on the developing fetus from in-utero exposure to cell phone radiation have been observed in both human and animal studies since 2006. Sources of fetal and neonatal exposures of concern include cell phone radiation (both paternal use of wireless devices worn on the body and maternal use of wireless phones during pregnancy). Sources include exposure to whole-body RFR from base stations and WI-FI, use of wireless laptops, use of incubators for newborns with excessively high ELF-EMF levels resulting in altered heart rate variability and reduced melatonin levels in newborns, fetal exposures to MRI of the pregnant mother, and greater susceptibility to

leukemia and asthma in the child where there have been maternal exposures to ELF-EMF. Divan et al (2008) found that children born to mothers who used cell phones during pregnancy develop more behavioral problems by the time they have reached school age than children whose mothers did not use cell phones during pregnancy. Children whose mothers used cell phones during pregnancy had 25% more emotional problems, 35% more hyperactivity, 49% more conduct problems and 34% more peer problems (Divan et al, 2008). Aldad et al (2012) showed that cell phone radiation significantly altered fetal brain development and produced ADHD-like behavior in the offspring of pregnant mice. Exposed mice had a dose-dependent impaired glutamatergic synaptic transmission onto Layer V pyramidal neurons of the prefrontal cortex. The authors conclude the behavioral changes were the result of altered neuronal developmental programming in utero. Offspring mice were hyperactive and had impaired memory function and behavior problems, much like the human children in Divan et al (2008). Fragopoulou et al (2012) reports that brain astrocyte development followed by proteomic studies is adversely affected by DECT (cordless phone radiation) and mobile phone radiation.
See www.bioinitiative.org Section 19 and 20 for references.

Fetal (in-utero) and early childhood exposures to cell phone radiation and wireless technologies in general may be a risk factor for hyperactivity, learning disorders and behavioral problems in school.

8. Evidence for Effects on Autism (Autism Spectrum Disorders)

"*Autism spectrum disorder (ASD), the fastest-growing complex neurodevelopment disorder, continues to rise in its prevalence, now affecting up to 1 in 50 children in the USA, and averaging 1% globally, according to the latest CDC report. More children will be diagnosed with ASD this year than with AIDS, diabetes & cancer combined in the USA.* ***ASD costs the nation $137 billion a year and this debt is expected to increase in the next decade.*** *Hence, ASD has become a huge healthcare burden and global threat, categorized by the CDC as a national public health crisis.*" (Special Issue on Autism, North American Journal of Medicine and Science, Vol 6, Issue 3, July 2013, Harvard Medical School).

Several thousand scientific studies over four decades point to serious biological effects and health harm from EMF and RFR. These studies report genotoxicity, single-and double-strand DNA damage, chromatin condensation, loss of DNA repair capacity in human stem cells, reduction in free-radical scavengers (particularly melatonin), abnormal gene transcription, neurotoxicity, carcinogenicity, damage to sperm morphology and function, effects on behavior, and effects on brain development in the fetus of human mothers that use cell phones during pregnancy. Cell phone exposure has been linked to altered fetal brain development and ADHD-like behavior in the offspring of pregnant mice.

Many disrupted physiological processes and impaired behaviors in people with ASDs closely resemble those related to biological and health effects of EMF/RFR exposure. Biomarkers and indicators of disease and their clinical symptoms have striking similarities. At the cellular and molecular level many studies of people with ASDs have identified oxidative stress and evidence of free-radical damage, as well as deficiencies of antioxidants such as glutathione. Elevated intracellular calcium in ASDs can be associated with genetic mutations but more often may be downstream of inflammation or chemical exposures. Lipid peroxidation of cell membranes, disruption of calcium metabolism, altered brain wave activity and consequent sleep, behavior and

immune disfunction, pathological leakage of critical barriers between gut and blood or blood and brain may also occur. Mitochondria may function poorly, and immune system disturbances of various kinds are common. Changes in brain and autonomic nervous system electrophysiology can be measured and seizures are far more common in ASCs than in the population at large. Sleep disruption and high levels of stress are close to universal in ASCs. All of these phenomena have also been documented to result from or be modulated by EMF/RFR exposure. Reducing or removing EMF and wireless RFR stressors from the environment is a reasonable precautionary action given the overall weight of evidence for a link to ASDs. The FCCs thermal safety limits do not address low-intensity (non-thermal) effects. The evidence is now overwhelming that limiting exposures to those causing thermal injury alone does not address the much broader array of risks and harm now clearly evident with chronic exposure to low-intensity (non-thermal) EMF/RFR. The now well-documented genotoxic impacts of EMF/RFR, placed in parallel with the huge rise in reported cases of ASCs as well as with the de novo mutations associated with some cases of ASCs (as well as other conditions), make it urgent to address the issue of (environmental) acquired as well as inherited genetic damage. With the rising numbers people with ASCs and other childhood health and developmental disorders, and with emerging evidence that EMF/RFR is a preventable environmental exposure of consequence to ASCs; public safety limits must be rethought in terms of fetal, neonatal and childhood neurological and electrophysiological development. The evidence is sufficient to warrant new public exposure standards benchmarked to low-intensity (non-thermal) exposure levels causing biological disruption and strong, interim precautionary practices are advocated. See www.bioinitiative.org Section 20 for references.

9. FCC Dockets 13-84, 03-137 and 13-39 propose to significantly relax rather than tighten exposure standards, in stark contrast to what the scientific evidence suggests is needed to protect public health from RFR. IEEE/FCC public safety limits remain unchanged and are still inadequate and obsolete with respect to prolonged, low-intensity NIER exposures.

Respectfully submitted:

Cindy Sage, Sage Associates 1396 Danielson Road, Santa Barbara, CA 93108
E-mail: sage@silcom.comTel.: 805-969-0557

Prof. Lennart Hardell, MD. PhD, Department of Oncology
Orebro University Hospital Orebro, Sweden
E-mail: lennart.hardell@orebroll.se

Dr. Martha Herbert, PhD, MD, Pediatric Neurology
TRANSCEND Research Program
Massachusetts General Hospital
Harvard Medical School Boston, MA USA
Email: drmarthaherbert@gmail.com

Exhibit A

Reported Biological Effects from Radiofrequency Radiation at Low-Intensity Exposure (Cell Tower, Wi-Fi, Wireless Laptop and 'Smart' Meter RF Intensities (Pages 1 – 11)

http://www.bioinitiative.org/rf-color-charts/ DOWNLOAD RF Color Charts

Reported Biological Effects from Radiofrequency Radiation at Low-Intensity Exposure
(Cell Tower, Wi-Fi, Wireless Laptop and 'Smart' Meter RF Intensities)

Power Density (Microwatts/centimeter2 - uW/cm2)		Reference
As low as (10^{-15}) or 100 femtowatts/cm2	Super-low intensity RFR effects at MW reasonant frequencies resulted in changes in genes; problems with chromatin conformation (DNA)	Belyaev, 1997
5 picowatts/cm2 (10^{-12})	Changed growth rates in yeast cells	Grundler, 1992
0.1 nanowatt/cm2 (10^{-10}) or 100 picowatts/cm2	Super-low intensity RFR effects at MW reasonant frequencies resulted in changes in genes; problems with chromatin condensation (DNA) intensities comparable to base stations	Belyaev, 1997
0.00034 uW/cm2	Chronic exposure to mobile phone pulsed RF significantly reduced sperm count,	Behari, 2006
0.0005 uW/cm2	RFR decreased cell proliferation at 960 MHz GSM 217 Hz for 30-min exposure	Veltzarov, 1999
0.0006 - 0.001 uW/cm2	Chronic exposure to base station RF (whole-body) in humans showed increased stress hormones; dopamine levels substantially decreased; higher levels of adrenaline and nor-adrenaline; dose-response seen; produced chronic physiological stress in cells even after 1.5 years.	Buchner, 2012
0.0006 - 0.0128 uW/cm2	Fatigue, depressive tendency, sleeping disorders, concentration difficulties, cardio- vascular problems reported with exposure to GSM 900/1800 MHz cell phone signal at base station level exposures.	Oberfeld, 2004
0.0009 uW/cm2	RFR induced 10%-40% increase in DNA synthesis in glioma cells (brain)	Stagg, 1997
0.003 - 0.02 uW/cm2	In children and adolescents (8-17 yrs) short-term exposure caused headache, irritation, concentration difficulties in school.	Heinrich, 2010
0.003 to 0.05 uW/cm2	In children and adolescents (8-17 yrs) short-term exposure caused conduct problems in school (behavioral problems)	Thomas, 2010
0.005 uW/cm2	In adults (30-60 yrs) chronic exposure caused sleep disturbances, (but not significantly increased across the entire population)	Mohler, 2010
0.005 - 0.04 uW/cm2	Adults exposed to short-term cell phone radiation reported headaches, concentration difficulties (differences not significant, but elevated)	Thomas, 2008
0.01 - 0.11 uW/cm2	RFR from cell towers caused fatigue, headaches, sleeping problems	Navarro, 2003

Stress proteins, HSP, disrupted immune function	Brain tumors and blood-brain barrier
Reproduction/fertility effeccts	Sleep, neuron firing rate, EEG, memory, learning, behavior
Oxidative damage/ROS/DNA damage/DNA repair failure	Cancer (other than brain), cell proliferation
Disrupted calcium metabolism	Cardiac, heart muscle, blood-pressure, vascular effects

Exhibit B

Reference List
Reported Biological Effects from Radiofrequency Radiation (RFR) at Low-Intensity Exposure Levels

(Cell Tower, WI-FI, Wireless Laptop, Wireless Utility Meters 'smart meters')

http://www.bioinitiative.org/bibliography/ DOWNLOAD REFERENCE LIST (PDF)

Acherman P et al, 2000. Exposure to pulsed high-frequency electromagnetic field during waking affects human sleep EEG. NeuroReport 11(15):3321-3325.

Adey,WR et al, 1999. Incidence of spontaneous and nitrosourea-induced primary tumors of the central nervous system in Fischer 344 rats chronically exposed to modulated microwaves. Radiation Research 152: 293-302.

Agarwal A, Deepinder F, Sharma RK, Ranga G, Li J. 2008. Effect of cell phone usage on semen analysis in men attending infertility clinic: an observational study. Fertil Steril. 89(1):124-8.

Agarwal A, Desai NR, Makker K, Varghese A, Mouradi R, Sabanegh E, Sharma R. 2009. Effects of radiofrequency electromagnetic waves (RF-EMW) from cellular phones on human ejaculated semen: an in vitro pilot study. Fertil Steril. 92(4) 1318-1325.

Aitken RJ, Bennetts LE, Sawyer D, Wiklendt AM, King BV. 2005 Impact of radio frequency electromagnetic radiation on DNA integrity in the male germline 28:171-179.

Akoev, IG et al, 2002. Enzymatic activity of some tissues and blood serum from animals and humans exposed to microwaves and hypothesis on the possible role of free radical processes in the nonlinear effects and modification of emotional behavior of animals. Radiats Biol Radioecol, 42(3):32-330.

Atasoy HI, Gunal MY, Atasoy P, Elgun S, Bugdayci G. 2012 Immunohistopathologic demonstration of deleterious effects on growing rat testes of radiofrequency waves emitted from conventional Wi-Fi devices. J Pediatr Urol. [Epub ahead of print]

Avendano C, Mata A, Sanchez Sarmiento CA, Doncei GF. 2012. Use of laptop computers connected to internet through Wi-Fi decreases human sperm motility and increases sperm DNA fragmentation. Fertility and Sterility. American Society for Reproductive Medicine, Published by Elsevier Inc. doi:10.1016/j.fertnstert.2011.10.012.

Beason, RC & Semm, P, 2002. Responses of neurons to an amplitude modulated microwave stumuls. Neuroscience Letters 333:175-178.

Behari J, Kesari KK 2006. Effects of microwave radiations on reproductive system of male rats. Embryo Talk 1 (Suppl.1):81-5.

Belokrinitsky, VS, 1982,. Destructive and reparative processes in hippocampus with long-term exposure to nonionizing radiation. In: U.S.S.R. Report, Effects of Nonionizing Microwave Radiation, No. 7, JPRS 81865, pp. 15-20.

Belyaev IY, Alipov YD, Harms-Ringdahl M. 1997. Effects of zero magnetic field on the conformation of chromatin in human cells. Biochim Biophys Acta 1336(3):465-473.

Belyaev IY, Hillert L, Protopopova M, Tamm C, Malmgren LO, Persson BR, Selivanova G, Harms-Ringdahl M. 2005. 915 MHz microwaves and 50 Hz magnetic field affect chromatin conformation and 53BP1 foci in human lymphocytes from hypersensitive and healthy persons. Bioelectromagnetics. 26(3):173-184.

Belyaev IY, Markova E, Hillert L, Malmgren LOG, Persson BRR. 2009. Microwaves from UMTS/GSM mobile phones induce long- lasting inhibition of 53BP1/γ-H2AX DNA repair foci in human lymphocytes. Bioelectromagnetics 30(2):129-41.

Bolshakov, MA & Alekseev, SI, 1992. Bursting responses of Lymnea neurons to microwave radiation. Bioelectromagnetics 13(2): 119-129.

Borbely, AA et al, 1999. Pulsed high-frequency electromagnetic field affects human sleep and sleep electroencephalogram. Neuroscience Letters 275(3): 207-210.

Boscolo et al, 2001. Effects of electromagnetic fields produced by radiotelevision broadcasting stations on the immune system of women. Sci Total Environ 273(1-3):1-10.

Buchner K, Eger H., 2011. Changes of Clinically Important Neurotransmitters under the Influence of Modulated RF Fields—A Long-term Study under Real-life ConditionsUmwelt-Medizin-Gesellschaft 24(1): 44-57. Original study in German.

Chia SE et al, 2000. Prevalence of headache among handheld cellular telephone users in Singapore: A Community Study. Environmental Health Perspectives 108(11):1059-1062.

Chiang, H et al, 1989. Health effects of environmental electromagnetic fields. Journal of Bioelectricity 8: 127-131.

Chou, CK et al, 1992. Long-term low level microwave irradiation of rats. Bioelectromagnetics 13:469-496.

Czyz J et al, 2004. High frequency electromagnetic fields (GSM signals) affect gene expression levels in tumor suppressor p53-deficient embryonic stem cells. Bioelectromagnetics 25: 296-307.

Dasdag, S et al, 1999. Whole-body microwave exposure emitted by cellular phones and testicular function of rats. Urological Research 27(3):219-223.

D'Costa, H et al. 2003. Human brain wave activity during exposure to radiofrequency field emissions from mobile phones. Australasian Physical & Engineering Sciences in Medicine, Vol. 26, No. 4

De Pomerai, D et al, 2000. Non-thermal heat-shock response to microwaves. Nature 405: 417-418.

D'Inzeo, G et al, 1988. Microwave effects on acetylcholine-induced channels in cultured chick myotubes. Bioelectromagnetics 9: 363-372.

De Iuliis GN, Newey RJ, King BV, Aitken RJ. 2009. Mobile phone radiation induces reactive oxygen species production and DNA damage in human spermatozoa in vitro. PLoS One 4(7):e6446.

Dolk, H et al, 1997. Cancer incidence near radio and television transmitters in Great Britain. American Journal of Epidemiology 145(1): 1-9.

Dumansky, JD & Shandala, MG, 1974. The biological action and hygenic significance of elecromagnetic fields of superhigh and ultrahigh frequencies in densely populated areas. In: Biological Effects and Health Hazards of Microwave Radiation. Proceedings of an International Symposium, Czerski, P et al, (Eds) Warsaw, 15-18 October 1973, Polish Medical Publishers.

Dutta, SK et al, 1989. Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture. Bioelectromagnetics 10: 197-202.

Elekes, E, 1996. Effect on the immune system of mice exposed chronically to 50 Hz amplitude-modulated 2.45 GHz microwaves. Bioelectromagnetics 17:246-248.

Eltiti S, Wallace D, Ridgewell A, Zougkou K, Russo R, Sepulveda F, Mirshekar-Syahkal D, Rasor P, Deeble R, Fox E. 2007. Does short-term exposure to mobile phone base station signals increase symptoms in individuals who report sensitivity to electromagnetic fields? A double-blind randomized provocation study. Environ Health Perspect 115(11): 1603-8.

Eltiti S, Wallace D, Ridgewell A, Zougkou K, Russo R, Sepulveda F, Fox E. 2009. Short-term exposure to mobile phone base station signals does not affect cognitive functioning or physiological measures in individuals who report sensitivity to electromagnetic fields and controls. Bioelectromagnetics 30(7):556-63.

Federal Communications Commission, 1997. OET Bulletin 65: 1997-01

Fesenko, EE et al, 1999. Microwaves and cellular immunity. I. Effect of whole body microwave irradiation on tumor necrosis factor production in mouse cells. Bioelectrochemistry and Bioenergetics 49 (1): 29-35.

Fragopoulou AF, Koussoulakos SL, Margaritis LH. 2010. Cranial and postcranial skeletal variations induced in mouse embryos by mobile phone radiation. Pathophysiology. 17(3):169-77.

Garaj-Vrhrovac, V et al, 1999. Micronucleus assay and lymphocyte mitotic activity in risk assessment of occupational exposure to microwave radiation. Chemosphere 39 (13) 2301-2312.

Grundler W, Kaiser F, Keilmann F, Walleczek J. 1992. Mechanisms of electromagnetic interaction with cellular systems. Naturwissenschaften 79(12):551-9.

Gul A, Celebi H, Uğraş S.2009. The effects of microwave emitted by cellular phones on ovarian follicles in rats. Arch Gynecol Obstet. 280(5):729-33,

Hamblin, D. et al, 2004. Examining the effects of electromagnetic fields emitted by GSM mobile phones on human event-related potentials and performance during an auditory task. Clinical Neurophysiology 115:171-178.

Hamnerius, Y, 2000. Microwave exposure from mobile phones and base stations in Sweden. International Conference on Cell Tower Siting, June 7-8, 2000, Sponsored by the University of Vienna & LandSalzburg, Salzburg, Austria.

Heinrich S, Thomas S, Heumann C, von Kries R, Radon K. 2010. Association between exposure to radiofrequency electromagnetic fields assessed by dosimetry and acute symptoms in children and adolescents: a population based cross-sectional study. Environ Health 9:75.

Hjollund NH, Bonde JP, Skotte J, 1997 Semen analysis of personnel operating military radar equipment. Reprod Toxicol 11(6):897

Hocking, B et al, 1996. Cancer incidence and mortality and proximity to TV towers Medical Journal of Australia 165(11-12): 601-605.

Hocking, B et al, 2000. Decreased survival for childhood leukemia in proximity to TV towers. Poster presented at the Annual Scientific Meeeting of the Royal Australian College of Physicians in Adelaide, SA, Australia, May 2000.

Huber, R et al, 2002. Electromagnetic fields, such as those from mobile phonesm alter regional cerebral blood flow and sleep and waking EEG. J. Sleep Res. 11: 289-295.

Hutter HP, Moshammer H, Wallner P. Kundi M. 2006. Subjective symp- toms, sleeping problems, and cognitive performance in subjects living near mobile phone base stations, Occup. Environ. Med. 63. 307–313.

IEEE, 1999. C95: 1-1999(US)

Ilhan A, Gurel A, Armutcu F, Kamisli S, Iraz M, Akyol O, Ozen S. 2004, Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. Clin Chim Acta. 340(1-2): 153-162.

Ilhan, A et al. 2004. Ginkgo biloba prevents mobile phone-induced oxidative stress in rat brain. Clinica Chimica Acta 340, 153-162.

Ivaschuk, OI et al, 1997. Exposure of nerve growth factor-treated PC 12 rat pheochromocytoma cells to a modulated radiofrequency field at 836.55 MHz: effects on c-jun and c-fos expression. Bioelectromagnetics 18 (3): 223-229.

Kesari KK, Behari J. 2012 Evidence for mobile phone radiation exposure effects on reproductive pattern of male rats: Role of ROS. Electromagn Biol Med. 31(3):213-22.

Kong X, McDougle CJ (Editors). Preface. Special Issue on Autism, North American Journal of Science and Medicine, July 2013 (Volume 6, Issue 3)
http://najms.net/wp-content/uploads/v06i03.pdf

Khurana VG, Hardell L, Everaert J, Bortkiewicz A, Carlberg M, Ahonen M. 2010. Epidemiological evidence for a health risk from mobile phone base stations. Int J Occup Environ Health. 16(3):263-267.

Koivisto, M et al, 2000a. Effects of 902 MHz electromagnetic field emitted by cellular telephones on response times in humans. Neuroreport 11: 413-415.

Koivisto, M et al, 2000b. The effects of electromagnetic field emitted by GSM phones on working memory. Neuroreport 11:1641-1643.

Kolodynski, AA, & Kolodynska VV, 1996. Motor and psychological functions of school children living in the area of the Skrunda radio location station in Latvia. Science of the Total Environment 180:87-93.

Krause, CM et al, 2000. Effects of electromagnetic field emitted by a cellular phone on the EEG during a memory task. Neuroreport 11:761-764.

Kues, HA et al, 1992. Increased sensitivity of the non-human primate eye to radiation following opthalmic drug pretreatment. Bioelectromagnetics 13:379-393.

Kumar S Behari J Sisodia R. 2012. Impact of Microwave at X-Band in the aetiology of male infertility. Electromagnetic Biology and Medicine, 31(3): 223–232. online DOI: 10.3109/15368378.2012.700293.

Kundi M. Hutter HP. 2009. Mobile phone base stations—Effects on wellbeing and health. Pathophysiology 16 123–135.

Kwee, S et al, 1997. The biological effects of microwave radiation. Proceedings of the Second World Congress for Electricity and Magnetism in Biology and Medicine, Bologna, Italy, June 1997.

Kwee, S et al, 2001. Changes in cellular protiens due to environmental non-ionizing radiation. I. Heat-shock protiens. Electro-and Magnetobiology 20:141-152.

Lai H, & Singh, NP, 1996. Single and double strand DNA breaks in rat brain cells after acute exposure to radiofrequency electromagnetic radiation. International Journal of Radiation Biology 69:513-21.

Lass, J et al, 2002. Effects of 7 Hz-modulated 450 MHz electromagnetic radiation on human performance in visual memory tasks. Int. J. Radiat. Biol. 73(10): 937-944.

Lebedeva NN et al, 2000. Cellular phone electromagnetic field effects on bioelectric activity of human brain. Crit Rev Biomed Eng 28(1-2) 323-337.

Leszczynski, D et al, 2002. Non-thermal activation of the hsp27/p38MAPK stress pathway by mobile phone radiation in the human endothelial cells: Molecular mechanism for cancer- and blood-brain barrier-related effects. Differentiation 70: 120-129.

Leszczynski, D et al, 2004. Proteomics analysis of human endothelial cell line EA.hy926 after exposue to GSM 900 radiation. Short Communication. Proteomics 4, 1359-1365.

Lu, ST et al, 1999. Ultrawide-band electromagnetic pulses induced hypotension in rats. Physiology and Behavior, 67:753-761.

Magras, IN & Zenos, TD, 1997. RF Radiation-induced changes in the prenatal development of mice. Bioelectromagnetics 18:455-461.

Mann, K et al, 1996. Effects of pulsed high-frequency electromagnetic fields on human sleep. Neuropsychobiology 33:41-47.

Mann, K et al, 1998. Effects of pulsed high-frequency electromagnetic fields on the neuroendocrine system. Neuroendocrinology 67: 139-144.

Mantiply, ED et al, 1997. Summary of measured radiofrequency electric and magnetic fields (10 kHz to 30 GHz) in the general and work environment. Bioelectromagnetics 18: 563-577.

Markova E, Hillert L, Malmgren L, Persson BRR, Belyaev IY. 2005. Microwaves from GSM mobile telephones affect 53BP1 and y-H2AX foci in human lymphocytes from hypersensitive and healthy persons. Environmental Health Perspectives Vol 113: No. 91 1172-1177

Marinelli, F La Sala D Ciccciotti G Cattini L Trimarchi C Putti S Zamparelli A Giuilani L Tomassetti G Cinti C. 2004. Exposure to 900 MHz Electromagnetic Field induces an unbalance between pro-apoptotic and pro-survival signals in T-lymphoblastoid leukemia CCRF-CEM cells. Journal of Cellular Physiology 198: 324 – 332.

Mohler E, Frei P, Braun-Fahrländer C, Fröhlich J, Neubauer G, Röösli M; Qualifex Team. 2010. Effects of everyday radiofrequency electromagnetic-field exposure on sleep quality: a cross-sectional study. Radiat Res 174(3):347-56.

Oberfeld, G Enrique, NA Manuel P Ceferino M Gomez-Perrretta C. 2004. The Microwave Syndrome – Further Aspects of a Spanish Study. 3rd International Workshop on Biological Effects of Electromagnetic Fields. Kos, Greece.

Otitoloju AA, Obe IA, Adewale OA, Otubanjo OA, Osunkalu VO. 2010. Preliminary study on the induction of sperm head abnormalities in mice, Mus musculus, exposed to radiofrequency radiations from global system for mobile communication base stations. Bulletin of Environmental Contamination and Toxicology 84(1):51-4.

Navakatikian, MA & Tomashevskaya, LA, 1994 Phasic behavioral and endocrine effects of microwaves of nonthermal intensity. In: Biological Effects of Electric and Magnetic Fields, Volume 1, Carpenter, DO, (Ed.) Academic Press, Inc., San Diego, CA., pp. 333-342.

Navarro EA, Sequra J, Portoles M, Gomez-Perretta de Mateo C. 2003. The Microwave Syndrome: A Preliminary Study in Spain. Electromag Biol Med 22:161-169,

Novoselova, EG et al, 1999. Microwaves and cellular immunity. II Immunostimulating effects of microwaves and naturally occurring antioxident nutrients. Bioelectrochemistry and Bioenergetics 49 (1): 37-41.

Panagopoulos DJ. 2012. Effect of microwave exposure on the ovarian development of Drosophila melanogaster. Cell Biochem Biophys. 63(2):121-132,.

Paulraj R, Behari J. 2004. Radio frequency radiation effects on protein kinase C activity in rats' brain. Mutat Res. 545(1-2):127-130,

Persson, RR et al, 1997. Blood-brain barrier permeability in rats exposed to electromagnetic fields used in wireless communication. Wireless Networks 3:455-461.

Paredi P et al, 2001. Local Vasodilator Response to Mobile Phones. Laryngoscope 111: 159-162.

Phillips, J et al, 1998. DNA damage in molt-4 lymphoblastoid cells exposed to cellular telephone radiofrequency fields in vitro. Bioelectrochemistry and Bioenergetics 45:103-110.

Preece. A et al, 1999. Effect of a 915-MHz simulated mobile phone signal on cognitive function in man. International Journal of Radiation Biology 75: 447-456.

Pyrpasopoulou, A et al, 2004. Bone morphogenetic protein expression in newborn rat kidneys after prenatal exposure to radiofrequency radiation. Bioelectromagnetics 25: 216-227.

Ray, S & Behari, J, 1990. Physiological changes in rats after exposure to low levels of microwaves. Radiation Research 123: 190-202.

Repacholi, M. et al, 1997. Lymphomas in Eμ-Pim1 transgenic mice exposed to pulsed 900 MHz electromagnetic fields. Radiation Research 147:31-40.

Richter, E et al, 2000. Cancer in radar technicians exposed to radiofrequency/microwave radiation: sentinel episodes. International Journal of Occupational Health 6(3): 187-193.

Riddervold IS, Pedersen GF, Andersen NT, Pedersen AD, Andersen JB, Zachariae R, Mølhave L, Sigsgaard T, Kjaergaard SK. 2008. Cognitive function and symptoms in adults and adolescents in relation to RF radiation from UMTS base stations. Bioelectromagnetics 29(4):257-67.

Sage Associates, 2004. An Overview of Low-Intensity Radiofrequency/Microwave Radiation Studies Relevant to Wireless Communications and Data. Bioelectromagnetics Society Annual Meeting, Washington DC, June 2004.

Sage Associates, 2004. Epidemiology for Decisionmakers: A Visual Guide to Residential and Occupational EMF Epidemiological Results on Leukemia 1979-2004.
International Conference on Leukemia, London, September 2004. Children with Leukemia Trust (UK Registered Charity No. 298405).

Sage Associates, 2000. An overview of radiofrequency/microwave radiation studies relevant to wireless communications and data. International Conference on Cell Tower Siting, Salzburg, Austria, Land Salzburg-Landessanitatsdirektion – Umweltmedizin, Federal State of Salzburg Public Health Department, Environmental Health Unit, June 7-8, 2000.

Salama N, Kishimoto T, Kanayama HO. 2010. Effects of exposure to a mobile phone on testicular function and structure in adult rabbit. Int J Androl. 33(1):88-94.

Salford, LG et al. 1994. Permeability of the blood brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50 and 200 Hz. Microscopy Research and Technique 27:535-542.

Salford, LG et al, 2003. Nerve cell damage in mammalian brain after exposure to microwaves from GSM mobile phones. Environmental Health Perspectives Online January 29.

Sandstrom M et al, 2001. Mobile phone use and subjective symptoms. Comparison of symptoms experienced by users of analogue and digital mobile phones. Occup Med 51(1) 25-35.

Santini R et al, 2001. Symptoms rapportes par des utilisateurs de telephones mobiles cellulaires. Path Biol 49:222-226.

Sarimov, R., Malmgren, L.O.G., Markova, E., Persson, B.R.R.. Belyaev, I.Y. 2004. Nonthermal GSM microwaves affect chromatin conformation in human lymphocytes similar to heat shock. IEEE Trans Plasma Sci 32:1600-1608,

Schirmacher, A et al, 2000. Electromagnetic fields (1.8 GHz) increase the permeability of sucrose of the blood-brain barrier in vitro. Bioelectromagnetics 21:338-345.

Schmidt M Murbach M Inelustenberger C Maire M Kuster N Achermann P. s2012. Sleep EEG alterations: effects of pulsed magnetic fields versus pulse-modulated radio frequency electromagnetic fields. J. Sleep Research, European Sleep Research Society DOI: 10.1111/j.1365-2869.2012.01025.x.

Schwartz, JL et al, 1990. Exposure of frog hearts to CW or amplitude-modulated VHF fields: selective efflux of calcium ions at 16Hz. Bioelectromagnetics 11(4): 349-358.

Seaman, RL et al, 1999. Hyperactivity caused by nitric oxide synthase inhibitor is countered by ultra-wide band pulses. Bioelectromagnetics 20: 431-439.

Somosy, Z et al, 1991. Effects of modulated and continuous microwave irradiation on the morphology and cell surface negative charge of 3T3 fibroblasts. Scanning Microsc 5(4):1145-1155.

Somosy, Z et al, 1993. Effects of modulated and continuous microwave irradiation on pyroantimonate precipitable calcium content in junctional complex of mouse small intestine. Scanning Microsc 7(4): 1255-1261.

Stagg RB et al, 1997. DNA synthesis and cell proliferation in C6 glioma and primary glial cells exposed to 836.55 MHz modulated radiofrequency field. Bioelectromagnetics 18(3):230-236.

Stang A et al, 2001. The possible role of radiofrequency radiation in the development of uveal melanoma. Epidemiology 12(1):7-12.

Stankiewicz W, Dąbrowski MP, Kubacki R, Sobiczewska E, Szmigielski S. 2006. Immunotropic Influence of 900 MHz Microwave GSM Signal on Human Blood Immune Cells Activated in Vitro. Electromagnetic Biology and Medicine 25(1) 45-51.

Stark KD et al, 1997. Absence of chronic effect of exposure to short-wave radio broadcast signal on salivary melatonin concentrations in dairy cattle. J Pineal Res 22(4):171:176.

Sun W, Shen X, Lu D, Fu Y, Chiang H. 2012. A 1.8-GHz radiofrequency radiation induces EGF receptor clustering and phosphorylation in cultured human amniotic (FL) cells. Int J Radiat Biol 88(3):239-44.

Szmigielski, S et al, 1982. Accelerated development of spontaneous and benzpyrene-induced skin cancer in mice exposed to 2350 MHz microwave radiation. Bioelectromagnetics 3: 179-192.

Tattersall, JE et al, 2001. Effects of low intensity radiofrequency electromagnetic fields on electrical activity in rat hippocampal slices. Brain Res 904(1): 43-53.

Thomas S, Kühnlein A, Heinrich S, Praml G, Nowak D, von Kries R, Radon K. 2008. Personal exposure to mobile phone frequencies and well-being in adults: a cross-sectional

study based on dosimetry. Bioelectromagnetics 29:463-470.

Thomas S, Heinrich S, von Kries R, Radon K. 2010. Exposure to radio-frequency electromagnetic fields and behavioural problems in Bavarian children and adolescents. Eur J Epidemiol 25(2):135-41.

TNO Physics and Electronics Laboratory, The Netherlands. 2003. Effects of Global Communication System radio-frequency fields on well-being and cognitive functions of human beings with and without subjective complaints. Netherlands Organization for Applied Scientific Research 1-63.

Trosic, I et al, 2002. Micronucleus induction after whole-body microwave irradiation of rats. Mutation Research 521: 73-79.

Velizarov, S et al, 1999. The effects of radiofrequency fields on cell proliferation are non-thermal. Bioelectrochemistry and Bioenergetics 48: 177-180.

Veyret, B et al, 1991. Antibody responses of mice exposed to low-power microwaves under combined, pulse and amplitude modulation. Bioelectromagnetics 12: 47-56.

Weisbrot, D et al, 2003. Effects of mobile phone radiation on reproduction and development in Drosophila melanogastor. Journal of Cellular Biochemistry 89: 48-55.

Wolke, S et al, 1996. Calcium homeostasis of isolated heart muscle cells exposed to pulsed high-frequency electromagnetic fields. Bioelectromagnetics 17(2): 144-153.

Yan JG, Agresti M, Bruce T, Yan YH, Granlund A, Matloub HS. 2007. Effects of cellular phone emissions on sperm motility in rats. Fertility and Sterility 88(4):957-64.

EXHIBIT E

EXHIBIT F

AMERICAN ASSOCIATION for JUSTICE

Formerly the Association of Trial Lawyers of America (ATLA®)

September 3, 2013

Federal Communications Commission
445 12th Street, SW, Room TW-A325
Washington, DC 20554

RE: Reassessment of Exposure to Radiofrequency Electromagnetic Fields Limits and Policies (Docket No. FCC-2013-0204)

To Whom It May Concern:

The American Association for Justice (AAJ), formerly the Association of Trial Lawyers of America (ATLA), hereby submits the organization's response to the Federal Communications Commission's (FCC) Notice of Inquiry on the subject of the biological effects of radiofrequency radiation and the reconsideration of current exposure limits. *See* 77 FR 33654.

AAJ, with members in the United States, Canada and abroad, is the world's largest trial bar. It was established in 1946 to safeguard victims' rights, strengthen the civil justice system, and protect access to the courts. In the nearly twenty years since the 1996 release of the FCC's Report and Order outlining the Commission's radiofrequency radiation exposure limits, the number of mobile phone calls per day, the length of each call, and the amount of time people spend using mobile phones have all increased.[1] Moreover, given the increasingly compact size of most cell phone models and standard mobile usage where personal devices are typically held directly against one's ear, the FCC standard is clearly outdated. AAJ urges the Commission to reevaluate its reliance on decades-old data in setting its radiofrequency radiation (RF) exposure limits. The Commission must also review recent scientific studies which demonstrate a connection between radiation exposure and the incidence of cancer. Finally, the recent FCC reclassification of the ear ("pinna") as an extremity, allowing exposure to higher levels of radiofrequency radiation, must be reversed, either through rescission of the Order or lowering overall exposure limits for extremities.

I. The FCC Must Performed Appropriate Due Diligence in Setting Standards for Exposure to Radiofrequency Radiation

In a 2005 DC Circuit case where the U.S. Chamber of Commerce petitioned for review of Securities and Exchange Commission (SEC) rulemaking, the court conducted a "consideration of costs" analysis in determining whether the agency's actions was consistent with the public

[1] Letter from the American Academy of Pediatrics to the FCC Commissioner, available at http://citizensforsafetechnology.org/uploads/scribd/AAP_07-12-12%20FCC%20cell%20phone%20radiation%20ltr.pdf.

www.justice.org • 777 6th Street, NW • Suite 200 • Washington, DC 20001 • 202-965-3500

interest.[2] The court considered two factors: (1) the ability of the SEC to develop new data or to consider existing empirical data in undertaking the rulemaking and (2) whether the SEC considered the costs of the conditions it was imposing.[3] While the Court in *Chamber of Commerce v. Securities and Exchange Commission* ultimately held that the SEC did not exceed its statutory authority, in the current case, the ready availability of scientific studies and the potentially devastating public health risks associated with prolonged human exposure to radiofrequency radiation both point to a different conclusion. Here, a cost-benefit analysis clearly indicates that the overall costs of regulation and potential burdens on industry pale in comparison to the Commission's duty to protect the members of the public, particularly in light of recent scientific studies.

A. Consideration of Empirical Data

In re-evaluating radiofrequency radiation exposure limits, the most urgent area in which current standards should be modified is the standard for extremities, particularly in light of the March 27, 2013 Order by the FCC reclassifying the ear as an extremity, subjecting it to nearly three times the level of radiation previously allowed.[4] The rationale of the FCC in adopting the extremity classification of the pinna is based on the determination of the IEEE which makes the argument that because the tissue composition of the pinna is similar to the other extremities, the ear should be classified accordingly and subject to the higher SAR threshold of 4W/kg.[5] Notably, the IEEE report itself admits calculations showing that the absorption of RF energy has a minimal impact on pinna temperature was subject to "limited experimental measurements" and that the "temperature effect on human pinna would *vary significantly* [emphasis added] from model to model of mobile phones because of differences in the heat generated by various devices."[6]

There are several problems with FCC's reliance on the determinations of the IEEE. First, the IEEE study was released in 2006 and the speed with which cell phone manufacturers innovate means that both mobile phone and wireless technology have undergone substantial changes. Data based on devices used nearly a decade ago should not be relied upon to determine current RF energy standards and in the past few years, a number of American and international health and scientific bodies have contributed to the debate over cell phone radiation and its possible link to cancer. The International Agency for Research on Cancer (IARC), part of the United Nations' World Health Organization, said in June 2011 that a family of frequencies that

---

[2] *Chamber of Commerce v. Securities and Exchange Commission*, 412 F.3d 133 (D.C. Cir. 2005).
[3] *Id.*
[4] "Proposed Changes in the Commission's Rules Regarding Human Exposure to Radiofrequency Electromagnetic Fields," Changing the Specific Absorption Rate (SAR) of 1.6 W/kg averaged over 1 gram of tissue to a SAR limit of 4 W/kg averaged over any 10 grams of tissue for extremities such as hands, wrists, feet, ankles, and pinnae. Federal Communications Commission ET Docket No.03-137, available at http://www.fcc.gov/document/fcc-review-rf-exposure-policies.
[5] IEEE Stud C95.1-2005, *IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 Ghz*, Rationale for applying the peak special-average SAR values for the extremities to the pinna: "The pinna consist of skin, cartilage, fat, nerves, blood vessels and muscle tissue, a composition similar to that of the extremities...Temperature increased in the pinna from heat generated in the device and from RF absorption are not harmful even if imposed on an initial pinna temperature that is close to body core temperature."
[6] *Id.*

includes mobile phone emissions is "possibly carcinogenic to humans."[7] The National Cancer Institute has stated that although studies have not demonstrated that RF energy from cell phone definitely causes cancer, more research is needed because cell phone technology and cell phone use are changing rapidly. These studies and others clearly demonstrate the need for further research into this area and highlight the importance of reassessing the FCC's order to determine if it is protective of human health.

In addition, despite sharing tissue composition similar to that of extremities, the IEEE study fails to address a significant difference between the pinna and the extremities of the human body such as the hand, feet, wrists, and ankles: the former's proximity to the brain. While the pinna may function as a barrier between RF radiation and the brain, it is composed of permeable cartilage and RF radiation, like sound waves, are guided from the projecting part of the ear which lies outside the head, to the inner ear canal before ultimately reaching the brain. To compare the pinna and the body's extremities is an over simplification and an inaccurate analogy in regards to the effect of exposure to RF radiation. In considering changes to its current RF exposure limit rules, the FCC should move towards a safer standard, one that takes into account the mounting evidence of adverse health effects caused by cell phone radiation exposure. AAJ proposes that one immediate change the Commission must make is to reverse the recent pinna reclassification which has the potential to create long-term public health consequences.

B. The Costs of Rule Implementation

The second prong of the *U.S. Chamber v. SEC* ruling considers the potential costs of the agency rulemaking.[8] There, the court considered efficiency, competition, and capital formation as negative outcomes from the proposed rule's redefinition of a company's board composition.[9] Here, a much greater urgency is warranted as potential costs must take into account the latency period between cell phone usage and the presentation of symptoms attributable to radiation as well as the disparate impact of radiation on children.

1. Latency

Diseases like brain cancer are known to exhibit a long latency period.[10] For example, the survivors of the atomic bombs that fell at the end of World War II did not demonstrate any increased rate of malignant cancers of the brain until four decades later.[11] Moreover, carcinogens such as tobacco were not firmly identified as increasing the risk of cancer until more than ten years after first usage.[12] The effects of long-term cell phone radiation exposure will likely follow this pattern as a Swiss personal monitoring study found that mobile phone use

---

[7] D.L. Davis, et al., Swedish Review Strengthens Grounds for Concluding that Radiation From Cellular and Cordless Phones is a Probable Human Carcinogen, Pathophysiology (2013), available at http://dx/doi/org/10/1016/j.pathophys.2013.001

[8] See *Chamber of Commerce* at 143.

[9] *Id.*

[10] *See* The Cell Phone Problem, Environmental and Human Health, Inc, Concerning the latency period of brain tumors: "Data from ionizing radiation studies indicate a brain tumor latency time of between 20 and 55 years." available at http://www.ehhi.org/reports/cellphones/cell_phone_report_EHHI_Feb2012.pdf.

[11] *See* Davis at 2.

[12] *Id.*

currently accounts for one-third of total exposures to wireless and microwave radiation.[13] With more than 5.9 billion reported mobile phone users worldwide, the impact of cell phone radiation taken in the aggregate, constitutes an environmental carcinogen whose risk still remains in the discovery process. At a time when cell phone use has become an ubiquitous part of everyday life yet manufacturers have little impetus to reduce RF emissions due to stagnant FCC exposure limits, AAJ urges the Commission to undertake a thorough and impartial review of its standards.

2. Disparate Effects of Radiation on Children and Long-Term Users

A second cause for concern is the impact of cell phone radiation on children and long-term mobile phone users. Today, cell phone usage begins at a much younger age than in past decades as mobile devices are relied upon for communication, entertainment, and even use as navigational tools. However, studies indicate that radiation may have a disparate impact on the youngest cell phone users as "[h]igh resolution computerized models based on real human imaging data suggest that the higher conductivity and higher permittivity in children's brain tissues, together with their thinner skulls and small heads, will lead to higher SARs in their brains from microwave frequencies when compared to adults."[14] Indeed, a recent study conducted by researchers from Tel Aviv University has established a clear connection between long-term cell phone users and molecular changes that can lead to cancer.[15] Comparing the salivary glands of 20 long-term cell phone users who averaged 30 hours of use per week over a span of 12 years with 20 deaf subjects who did not use cell phones, scientists found that the cell phone users' saliva indicated higher levels of oxidative stress, a process that is a "major risk factor for cancer."[16]

In a December 2012 letter to then Representative Dennis Kucinich supporting H.R. 6358, the *Cell Phone Right to Know Act*, the American Academy of Pediatrics argued that "[t]he differences in bone density and the amount of fluid in a child's brain compared to an adult's brain could allow children to absorb greater quantities of RF energy deeper into their brains than adults. It is essential that any new standards for cell phone or other wireless devices be based on protecting the youngest and most vulnerable populations to ensure they are safeguarded through their lifetimes."[17] Yet, not only does the FCC make no distinction between the levels of cell phone radiation advisable for children and for adults, the agency takes the opposite approach in its Order, reclassifying the pinna and effectively making cell phones less safe for the segment of the population most at risk for future harm. Before developing new limits on RF exposure, the FCC must conduct a thorough analysis into the long-term effects of radiofrequency emissions, particularly on children whose physiological make-up and overall lifetime exposure may warrant a separate and more conservative standard.

---

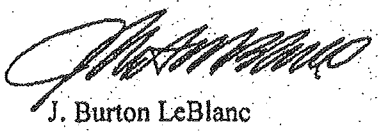
[13] *Id.* at 3.
[14] *Id.* at 4.
[15] "Put Away That Cell Phone: Israeli Study Highlights Cancer Risk," Times of Israel, July 20, 2013, available at http://www.timesofisrael.com/put-away-that-cellphone-israeli-study-highlights-cancer-risk/.
[16] *Id.*
[17] Letter from the American Academy of Pediatrics to Dennis Kucinich, available at http://ehtrust.org/wp-content/uploads/2012/12/aap_support_letter_cell_phone_right_to_know_act.pdf.

II. Conclusion

Nearly half of the world's mobile phone users are under the age of 30 and live in developing countries.[18] Moreover, even as the Davis study cautions that brain cancer is the "tip of the iceberg," the rest of the body is also showing effects other than cancers.[19] In the United States alone, the Central Brain Tumor Registry of the United States estimates that about 10,000 people will develop glioma, or tumor of the brain this year. Given the growing evidence of harm arising from human exposure to radiofrequency emissions, the FCC must lower its current exposure limits beginning with rescinding its Order reclassifying the pinna as an extremity, a rash decision which will put future generations at risk of an invisible but menacing carcinogen. AAJ urges the FCC to ensure public safety by committing to more robust exploration in this area.

AAJ appreciates this opportunity to submit comments in response to the Federal Communications Commission's Notice of Inquiry seeking input on whether its exposure limits should be more restrictive, less restrictive, or remain the same. If you have any questions or comments, please contact Ivanna Yang, AAJ's Assistant Regulatory Counsel at (202) 944-2806.

Sincerely,



J. Burton LeBlanc
President
American Association for Justice

[18] *See* Davis at 4.
[19] *Id.* at 1.

EXHIBIT F

ORIGINAL ARTICLE

Environmental risk factors for cancers of the brain and nervous system: the use of ecological data to generate hypotheses

Frank de Vocht,[1] Kimberly Hannam,[2] Iain Buchan[3]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/oemed-2012-100954).

[1]Centre for Occupational and Environmental Health, Institute for Population Health, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK
[2]Maternal and Fetal Health Research, Medical and Human Sciences, Manchester Academic Health Sciences Centre, University of Manchester, Manchester, UK
[3]NIBHI & NWeH Science, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, UK

Correspondence to
Dr Frank de Vocht, COEH, Institute for Population Health, Manchester Academic Health Sciences Centre, The University of Manchester, Oxford Road, Manchester M13 9PL, UK; frank.devocht@manchester.ac.uk

Received 29 May 2012
Revised 27 November 2012
Accepted 14 December 2012
Published Online First
23 January 2013

To cite: de Vocht F, Hannam K, Buchan I. *Occup Environ Med* 2013;**70**: 349–356.

ABSTRACT

Background There is a public health need to balance timely generation of hypotheses with cautious causal inference. For rare cancers this is particularly challenging because standard epidemiological study designs may not be able to elucidate causal factors in an early period of newly emerging risks. Alternative methodologies need to be considered for generating and shaping hypotheses prior to definitive investigation.

Objectives To evaluate whether open-access databases can be used to explore links between potential risk factors and cancers at an ecological level, using the case study of brain and nervous system cancers as an example.

Methods National age-adjusted cancer incidence rates were obtained from the GLOBOCAN 2008 resource and combined with data from the United Nations Development Report and the World Bank list of development indicators. Data were analysed using multivariate regression models.

Results Cancer rates, potential confounders and environmental risk factors were available for 165 of 208 countries. 2008 national incidences of brain and nervous system cancers were associated with continent, gross national income in 2008 and Human Development Index Score. The only exogenous risk factor consistently associated with higher incidence was the penetration rate of mobile/cellular telecommunications subscriptions, although other factors were highlighted. According to these ecological results the latency period is at least 11–12 years, but probably more than 20 years. Missing data on cancer incidence and for other potential risk factors prohibit more detailed investigation of exposure–response associations and/or explore other hypotheses.

Conclusions Readily available ecological data may be underused, particularly for the study of risk factors for rare diseases and those with long latencies. The results of ecological analyses in general should not be overinterpreted in causal inference, but equally they should not be ignored where alternative signals of aetiology are lacking.

What this paper adds

- This study shows how existing open-access online databases can be used to explore potential risk factors for rare diseases at an ecological level, and enables timely generation of hypotheses where standard epidemiological study designs may not be able to elucidate risk factors in an early period of emerging risks.
- We show a clear association between national penetration of cellular telecommunications subscriptions and higher incidence of brain and nervous system cancers, with a latency between exposure and clinical onset of at least 11–12 years, but probably more than 20 years.
- This methodology might be used more widely to test the generalisation of existing hypotheses and to generate new ones, especially for rare diseases, where definitive epidemiological studies are infeasible for addressing public health concerns in a timely manner.

INTRODUCTION

Environmental risk factors for cancers receive substantial public attention, and there is a public health need to balance timely generation of hypotheses with cautious causal inference. Cautious and thorough epidemiological studies are required to confirm a causal link between an exposure and a disease outcome. Such studies usually take a long time before the results are shared with the scientific and policy communities; meanwhile, public debates may ensue over the topic under investigation. In a more proactive approach, however, hypotheses about risk factors could be generated from available data that would enable more informed early debate under a precautionary principle. Moreover, faster generation of hypotheses based on routine data may better direct research resources at emerging risk factors.

For most common cancers the main risk factors are well established. This knowledge is largely based on classical study designs with sufficient statistical power to make confident causal inferences. For lung cancer, for example, the most frequently occurring cancer in the world, it is well established that the main risk factor is tobacco smoking, accounting for 75%–90% of the risk, while other main risk factors include exposure to radon, environmental tobacco smoke, asbestos and other occupational exposures.[1] However, for many cancers, especially the rarer ones, most of the aetiology is unknown and for many may involve a complex interaction of demographic, genetic, socioeconomic and environmental risk factors.

The multi-factorial initiation and development of cancers complicate strategies to prevent or reduce

the number of new cases. Epidemiological studies are generally designed to investigate one, or few hypotheses, rather than being of a wide exploratory or hypotheses generating nature. More hypothesis generating strategies are however emerging with the generation of large dataset from high-throughput *omics* and open linked data sources. Therefore, it is of interest to explore alternative methodologies for generating and shaping hypotheses prior to definitive investigation.

Here we consider the hypothesis generating potential[2] of an ecological combination of: (1) open data on incidence and mortality from cancers at national level for all countries of the world, which are available from the International Agency for Research on Cancer's (IARC) GLOBOCAN 2008 project[3] and (2) open information on putative risk factors and related confounding factors collected at a national level, available from the World Bank list of development indicators[4] and from the United Nations Development Report.[5] The approach may be especially useful in studies of rare cancers where it is difficult to obtain studies of sufficient size to study environmental and occupational risk factors. So, we evaluate this open ecological approach for the specific case study of environmental risk factors for malignant brain tumours.

Malignant brain tumours are considered a rare cancer in that they account for only 1%–2% of all cancers in adults.[6] Furthermore, the incidence has been increasing worldwide over the past 3 decades, especially in industrialised societies.[7–10] Ageing populations[9] and better diagnostic methods[11 12] have been related to the rising incidence. Exogenous risk factors, however, have been underinvestigated. The only established environmental risk factor for gliomas is ionising radiation exposure to the head and neck, while in contrast allergies are consistently inversely associated with glioma risk.[13] However, a large number of environmental risk factors have been proposed that may contribute to increasing brain cancer incidence.[6] These include exposure to pesticides,[14 15] metals,[16] polycyclic aromatic hydrocarbons,[17 18] solvents,[19] glues[20] and electromagnetic fields[21]—with radiofrequency exposure from mobile phones gaining most public attention.[22] Although these exogenous factors are potentially amendable to interventions, the studies linking them to brain cancers have been inconsistent in terms of causality.[16]

This absence of evidence provides an important context for the present study to evaluate the epidemiological worth of open data sources exploring potential risk factors at an ecological level to generate or shape hypotheses about possible causal mechanisms.

MATERIALS AND METHODS

Brain cancer incidence data

Data on incidence rates of cancers of the brain and nervous system for all countries of the world were obtained from the open, online GLOBOCAN 2008 resource.[3] Within the GLOBOCAN project, cancer statistics (including numbers of cases, incidence and mortality rates, and cumulative risk) are available at national and further aggregated levels. From here we extracted the age standardised, or age-world-standardised incidence rate (ASR(w)) per 100 000 population, based on weighted averages of the age-specific rates from the 'world standard population',[23] for cancers of the brain and nervous system in the year 2008.

The types of malignant neoplasms of the brain (C71) were coded using the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), and included neoplasms of the cerebrum (except lobes and ventricles) (C71.0), frontal lobe (C71.1), temporal lobe (C71.2), parietal lobe (C71.3), occipital lobe (C71.4), cerebral ventricle (excluding the fourth ventricle) (C71.5), cerebellum (C71.6), brain stem (C71.7), and neoplasms in overlapping lesions of the brain (C71.8) or unspecified (C71.9). Within the GLOBOCAN project, these are grouped together with malignant neoplasms of the meninges (C70), including neoplasms of the cerebral meninges (C70.0), spinal meninges (C70.1) and unspecified meninges (C70.9), and with malignant neoplasms of the nervous system (C72), which include neoplasms of the spinal cord (C72.0), cauda equine (C72.1), olfactory nerve (C72.2), optic nerve (C72.3), acoustic nerve (C72.4), other and unspecified cranial nerves (C72.5), and also overlapping lesions of brain and other parts of the central nervous system (C72.8) and unspecified central nervous system malignant neoplasms (C72.9).

Potential risk factor and confounder data

Data on potential risk factors or confounding factors were collected from two open resources: the World Bank list of development indicators[4] and the United Nations Development Report for Human Development Index (HDI)[5] statistics. Potential confounders were defined as available indicators that may (to some extent) account for differences in quality of cancer registration resulting in differences in incidence rates that are not due to differences between populations or risk factors between countries, or proxies thereof. From the list of development indicators, indicators that were included as potential confounders described population demographics, development and quality of healthcare (listed in table 1). Development indicators describing aspects of urbanisation, energy usage, distribution of occupational sectors or environmental/pollution factors were identified as potential environmental risk factors (listed in table 2). Data on each indicator were obtained for the year 2008. To investigate the latency between when biologically relevant exposure to one of the identified risk factors occurred and when the brain cancer was detected we also extracted risk factor data for the year 1998, and where possible additionally for the year 1995 (older data were not available on most risk factors).

Data treatment and statistical analyses

We linked the datasets by country. Of 208 countries, 23 had no data on risk factors, 10 did not have corresponding ASR(w)s and for 10 the ASR(w) was specified as an impossible '0'. These were removed prior to the analyses, resulting in a final sample of 165 countries. Similarly, indicators (risk or confounding factors) for which data were not available for more than 25% of countries were also deleted (completeness of total death reporting (percentage of reported total deaths to estimates total deaths) (missing=79), malnutrition prevalence-weight for age (percentage of children under 5) (missing=149), poverty headcount ratio at national poverty line (percentage of the population) (missing=125), physicians (per 1000) (missing=105), and public spending on education, total (percentage of government expenditure) (missing=104)).

Data were analysed using linear least-squares regression modelling in which the dependent variable ASR(w) being a rate, was $\log_e$-transformed to resemble a Gaussian distribution prior to statistical modelling. A level of $p<0.05$ was taken as evidence of statistical significant influence of an indicator on ASR(w), while $p<0.10$ was treated as 'borderline significance'.

Prior to adding risk factors in the analysis, a 'confounder model' was developed. All potential confounders were analysed separately in a univariate linear regression model and parameter estimates, statistical significance and explained variance (R^2) were registered. Subsequently, potential confounders with

Table 1 Univariate results potential confounding factors

Confounding factors	Corresponding World Bank indicator	1998 (p Value)*	2008 (p Value)*	Countries 1998	Countries 2008
Quality of cancer registration	Completeness of total mortality reporting (% of reported total deaths to estimates total deaths)		0.03 (<0.01)		80
Continent			p<0.01†		165
World (1st, 2nd, 3rd, other)			p<0.01†		165
Human Development Index			4.34 (p<0.01)	NA	154
Gender distribution	Population female (% total)	0.04 (0.30)	0.04 (0.20)	165	165
Age distribution	Population (0–14)	−0.07 (<0.01)	−0.07 (<0.01)	165	165
(% total)	Population (15–64)	0.11 (<0.01)	0.10 (<0.01)	165	165
	Population (>64)	0.14 (<0.01)	0.13 (<0.01)	165	165
General population health	Life expectancy at birth	0.08 (<0.01)	0.08 (<0.01)	162	165
	Mortality rate, under 5 (per 1000)	−0.01 (<0.01) ‡	−0.01 (<0.01)	163	163
	Survival to age 65 (% cohort) (f) §	0.05 (<0.01)	0.05 (<0.01)	165	165
	Survival to age 65 (% cohort) (m)§	0.04 (<0.01)	0.04 (<0.01)	165	165
	Malnutrition prevalence, weight for age (% children under 5)	−0.03 (0.01)¶	−0.09 (0.13)¶	49	5
	Birth rate, crude (per 1000 people)	−0.07 (<0.01)	−0.07 (<0.01)	164	165
	Mortality rate (per 1000) (f)	−0.01 (<0.01)	−0.01 (<0.01)	165	141
	Mortality rate (per 1000) (m)	−0.01 (<0.01)	−0.01 (<0.01)	165	141
Population wealth	Gross national income per capita (PPP ($))	0.00 (<0.01)	0.00 (<0.01)	151	156
	Poverty headcount ratio at national poverty line (% population)	NA	−0.02 (<0.01)	NA	30
Money spent on healthcare	Health expenditure per capita, PPP (constant 2005 international $)	0.00 (<0.01)	0.00 (<0.01)	161	160
	Health expenditure, public (% of government expenditure)	0.08 (<0.01)	0.04 (0.05)	160	161
	Physicians (per 1000)	0.36 (<0.01)	0.62 (<0.01)	76	51
Education	Public spending on education, total (% of government expenditure)	−0.02 (0.40)**	−0.06 (0.02)	80	53

*Dependent variable is log(e) transformed age-adjusted incidence rates per 100 000 population (ASR(w)).
†p Value based on ANOVA.
‡Year 2000 instead of 1998.
§Female (f) or male (m).
¶Years 2000 and 2009 instead of 1998 and 2008.
**Year 1999 instead of 1998.
ASR(w), Age-world-standardised incidence rate; NA, not available.

p values below 0.20 were added to a multiple regression confounder model using a forward selection method. Variables were subsequently kept in the model based on statistical significance ($p<0.05$) and decreased Bayesian Information Criterion. Multicollinearity was evaluated using Variance Inflation Factors (VIF), using a VIF above 10 as a rule of thumb for evidence of significant multicollinearity (realising that this cut-off should be interpreted with caution, so all situations were evaluated individually[24]) in which case the variable with lowest Bayesian Information Criterion was kept in the model. Model-fit was further evaluated by assessing distributions and trends of the residuals, half-normal probability plots and evaluation of influential observations using Cook's distance.

The 'risk factor' model was subsequently generated by adding independent risk factors to the final confounder model, using a similar model-building approach and evaluation criteria as described for the confounder model.

Additional exploratory and sensitivity analyses using the final model were done by stratification by continent, and by evaluation of different latencies (0–28 years). After obtaining the final multivariate regression model, the data were explored for non-linearity in covariate response by sequentially replacing each covariate by a quadratic cubic spline function using 1–3 knots using the *lmer* function in R.

RESULTS

Univariate analyses of all confounder and risk factor variables for the indicative years 1998 and 2008 indicate that many are, at face value, correlated to 2008 age-world standardised brain cancer incidence. These results are summarised in tables 1 and 2 for potential confounders and risk factors, respectively. For the majority, but not all, of the potential risk factors for which data were available from 1998, data were also available from 1995, and the results of these univariate analyses are provided in online supplementary table S1. Development of the multiple regression confounder model indicated many potential confounding factors were highly correlated with one another, but following the model-building strategy described above resulted in a confounder model that best described these data and included continent, 2008 gross national income and the HDI score as covariates (see online supplementary table S2). This confounder model explained about 67% of the variation between countries with the highest VIF of 5.22 for HDI, which indicated low to moderate multicollinearity only.

The univariate results for risk factors where data were available from 1995 and 1998 were largely similar, so to allow for another 3 years of latency the 1995 data of potential risk factors were subsequently added to the confounder model (table 3). These results indicate that ($p<0.10$) the national incidence of brain cancer is correlated to the proportion of people in large (>1 million people) urban agglomerations, but also to the percentage of the working population working in agriculture, electric power consumption, mobile cellular subscriptions (per 100 people), internet connections per 100 people, and the percentage of combustible renewables and waste (ie, solid biomass, liquid biomass, biogas, industrial waste and municipal waste) in

Table 2 Univariate results potential environmental risk factors

Risk factors	Corresponding World Bank indicator	1998 (p value)*	2008 (p value)*	Countries 1998	Countries 2008
Urbanisation (% population)	Urban population	0.02 (<0.01)	0.02 (<0.01)	165	165
	Population in urban agglomerations of more than 1 million	0.01 (0.09)	0.01 (0.20)	106	106
	Rural population	−0.02 (<0.01)	−0.02 (<0.01)	165	165
Energy usage	Energy use (kg of oil equivalent per capita)	0.00 (<0.01)	0.00 (<0.01)	129	129
Electrical usage	Electric power consumption (kWh per capita)	0.00 (<0.01)	0.00 (<0.01)	128	128
Cell phone use	Mobile cellular subscriptions (per 100 people)	0.04 (<0.01)	0.01 (<0.01)	162	163
Internet/broadband	Fixed broadband internet subscribers (per 100 people)	0.02 (0.99)	0.06 (<0.01)	52	161
	Internet users (per 100 people)	0.06 (<0.01)	0.03 (<0.01)	155	163
Employment (% total employment)	Agriculture	−0.01 (<0.01)	−0.02 (0.04)	84	26
	Industry	0.03 (<0.01)	−0.00 (0.95)	84	26
	Services	0.01 (0.07)	0.01 (0.05)	84	26
Environment/pollution					
Pesticides	Fertilizer consumption (kg per hectare of arable land)	NA	0.00 (0.03)	NA	139
Waste	Combustible renewable and waste (% of total energy)	0.00 (0.69)	−0.00 (0.57)	129	129
Organic water pollutant	Organic water pollutant (BOD) emissions (kg/day)	−5.29 (0.01)	NA	66	NA
Other greenhouse gas emissions	PFC/HFC/SF6 gas emissions (thousand metric tons of CO_2 equivalent)	0.00 (0.21)†	0.00 (0.22)†	129	129
	PM10, country level (ug/m^3)	−0.01 (<0.01)	−0.01 (0.01)	159	156
Traffic	Road sector gasoline Fuel consumption per capita (kt of oil equivalent)	0.00 (0.30)	0.00 (0.32)	128	129
	Road sector diesel fuel consumption per capita (kt of oil equivalent)	0.00 (0.15)	0.00 (0.08)	128	129
	Motor vehicles (per 1000)	NA	0.00 (<0.01)	NA	77
Smoking (% adults)	Smoking prevalence (f)		0.05 (<0.01)‡	NA	124
	Smoking prevalence (m)		0.03 (<0.01)‡	NA	127

*Dependent variable is log(e) transformed age-adjusted incidence rates per 100 000 population (ASR(w)).
†Years 2000 and 2005 instead of 1998 and 2008.
‡Year 2006 instead of 2008.
ASR(w), Age-world-standardised incidence rate; NA, not available; BOD, biochemical oxygen demand; PPP, purchasing power parity; ANOVA, analysis of variance; PFC, perfluorocarbons.

1995 but not 2008. Conversely, ASR(w) was further associated with the number of motor vehicles per 1000 people in 2008 but not in 1995. Note, however, that all associations were evaluated with varying numbers of countries where these data were collected. Further multiple regression modelling using the steps outlined above uncovered just one risk factor that was consistently correlated with increased incidence of cancers of the brain and central nervous system in 2008: the number of mobile phone subscriptions per 100 people (table 4), which indicated about a 4% increase in brain cancer incidence in 2008 for each additional per cent of mobile phone subscriptions in 1995 ($\beta \sim 0.04$ (SE$\sim$0.02), $p \sim 0.04$). Again, only low to moderate collinearity (VIF$\leq$6) between covariates was present. Additional stratification (table 5) by continent indicates that these trends can primarily be observed in European countries (although only Africa, Asia and Europe had data from enough countries). Crude associations between the one remaining significant risk factor, mobile phone subscriptions per 100 people, and ASR(w) are shown graphically in figure 1A,B.

Additional exploration of the latency period (figure 1D, and see online supplementary table S3), including the number of mobile subscribers per 100 people for each year between 1980 and 2008 (where possible) and brain cancer incidence in 2008, shows that statistical significant correlations could be observed until 1996. This was similar when all countries were used to analyse the effects of latency or only those 17 countries that had data on mobile phone subscriptions for 1995 (see online supplementary material).

Graphical assessment of the residuals (figure 1C) indicates a relatively good model fit of the final model, although some outliers are present. Sensitivity analyses using quadratic cubic splines to evaluate non-linearity in the confounder/exposure–response associations did not indicate improved fit of the models, based on Akaike Information Criterion values, or changes in the association between mobile phone penetration rate and brain cancer incidence. However, this could primarily be attributed to the relatively limited number of data points (data not shown).

DISCUSSION

In this study, we explored the epidemiological value of combining open data sources on cancer incidence from the GLOBOCAN project, development indicators from the World Bank list and United Nations to explore potential environmental risk factors of malignant neoplasms of the brain and central nervous system at an ecological level. This approach widened the generalisation of an existing hypothesis and highlighted new hypotheses for attention, and as such, this general approach may be applicable more widely, particularly to other rare diseases.

In our case study, cancers of the brain and nervous system represent a rare outcome, and relating it to mobile phone use at individual level is impractical due to: (1) the large numbers required to achieve sufficient statistical power; (2) problems with the accurate assessment of exposure;[25] and (3) difficulty in identifying controls given the advancing ubiquity of mobile phones. This work confirms that mobile phone use may be a risk factor, thereby confirming previous ecological findings from the USA.[26] Although our analyses indicate a relatively small risk, explaining only about 1% of the variation in incidence rates between countries, it is supported by data from individual-level studies.[27] A causal association, however, has not been confirmed by other studies[28–30] and remains controversial.[31–34] Overall,

Table 3 Risk factors added to confounder model

Environmental risk factor	Year	p Value	BIC	dF	VIF
Urban population (% total)*	2008	0.29	332.74	138	2.74
	1995	0.43	333.25	138	3.14
Population in urban agglomerations of more than 1 million (% of total population)	2008	0.01	210.36	86	2.39
	1995	0.01	181.72	87	2.50
Employment in agriculture (% of total employment)	2008	0.17	33.87	20	4.34
	1995	0.03	124.53	69	3.47
Employment in industry (% of total employment)	2008	0.90	36.42	20	2.14
	1995	0.06	125.71	69	1.71
Employment in services (% of total employment)	2008	0.36	35.30	20	3.73
	1995	0.26	128.34	69	4.17
Energy use (kg of oil equivalent per capita)	2008	0.98	251.25	108	2.31
	1995	0.86	251.21	108	4.33
Electric power consumption	2008	0.23	249.62	108	2.00
	1995	0.03	281.27	117	3.76
Mobile cellular subscriptions (per 100 people)	2008	0.28	323.86	136	3.91
	1995	0.04	322.89	135	2.67
Internet connections per 100 people	2008	0.32	327.43	136	7.41
	1995	0.04	216.57	97	1.75
Fertilizer consumption (kg per hectare of arable land)	2008	0.61	287.84	116	1.48
	1995	NA			
Combustible renewables and waste (% of total energy)	2008	0.32	250.15	108	1.10
	1995	0.06	247.34	108	3.98
Organic water pollutant (BOD) emissions (kg/day)	2008	NA			
	1995	0.15	93.60	36	1.19
Greenhouse gases (PFC /HFC/SF6 gas emissions (thousand metric tons of CO_2 equivalent))	2000	0.90	251.23	108	1.43
	1995	0.76	251.16	108	1.39
Road sector gasoline fuel consumption per capita (kt of oil equivalent)	2008	0.91	251.23	108	1.62
	1995	0.19	249.34	108	5.59
Road sector diesel fuel consumption per capita (kt of oil equivalent)	2008	0.83	251.20	108	1.41
	1995	0.62	250.97	108	2.72
Motor vehicles (per 1000)	2008	0.07	135.89	64	6.05
	1995	NA			
PM_{10}, country level ($\mu g/m^3$)	2008	0.52	323.26	132	1.33
	1995	0.42	325.31	134	1.51
Smoking prevalence (% adults) (female)	2006	0.66	257.97	103	3.95
	1995	NA			
Smoking prevalence (% adults) (male)	2006	0.42	259.19	105	2.42
	1995	NA			

*Note that urban population (% total) and rural population (% total) add up to 100%, so rural variable not added.
BIC, Bayesian Information Criterion; NA, not available; VIF, Variance Inflation Factors.

Table 4 Final multivariate results

R^2_{adj} ~0.68	BIC ~322.89	dF=135			
ANOVA	**dF**	**SS**	**F value**	**Pr>F**	**R^2**
GNI.08	1	51.508	134.193	<0.01	0.04
Continent	7	55.012	20.475	<0.01	0.09
HDI	1	13.505	35.183	<0.01	0.09
cellphone.95	1	1.606	4.185	0.043	0.01
Residuals	135	51.817			
Variable		**β**	**SE**	**p Value**	**VIF**
Intercept		−1.81	0.28	<0.01	
GNI.08		−0.00	0.00	<0.01	6.02
Continent	Asia	0.70	0.18	<0.01	2.26
	Central Americas	0.75	0.27	0.01	1.47
	Caribbean	0.46	0.30	0.12	1.33
	Europe	1.29	0.23	<0.01	3.86
	North America	0.91	0.44	0.04	1.49
	Oceania	−0.18	0.34	0.60	1.18
	South America	0.48	0.25	0.06	1.80
	Africa	–	–	–	
HDI		3.92	0.64	<0.01	5.29
cellphone.95		0.04	0.02	0.04	2.67

BIC, Bayesian Information Criterion; cellphone.95, mobile cellular subscriptions (per 100 people) in 1995; GNI, gross national income; GNI.08, gross national income per capita (2008); HDI, Human Development Index; VIF, Variance Inflation Factors.

however, the conclusion of the International Agency for Research on Cancer Monograph working group indicated that limited evidence for an association existed.[22] Our analyses further suggest that the latency between relevant exposure (mobile phone use) and clinical manifestation of the disease (brain and nervous system malignancies) is (at population level) at the very least 11–12 years but should ideally be more than 20 years, which is not reflected in most study designs.

Mobile phone use may be a proxy for another risk factor that correlates with mobile phone use but was not included in the available databases, or was available but was of inferior quality. Given that correlations were also noted in intermediate analyses for national electricity consumption, internet usage and population in urban agglomerations of more than 1 million we hypothesise that if this is the case, this is most likely to be some, yet unknown, factor related to urbanisation and development. However, given that mobile phone use both remained a significant factor independent of the inclusion of other potential risk factors in multivariate modelling and is also in broad agreement with some analytical studies to us indicates this may well be the most important exposure for further study; in agreement with conclusions reached by others.

Our approach further highlighted several other potential risk factors that may be associated with increased risk of brain cancer, namely: populations in urban agglomerations of more than 1 million; percentage of the working population employed in agriculture; percentage of the working population employed in industry; national electricity consumption; internet usage; and combustible renewables and waste. A correlation between urbanisation/population density and increased brain cancer risk has been reported before[35 36] but is inconsistent with other data[37 38]

Table 5 Stratification by continent (cell phone use in 1995)

Continent	β*	SE	p Value	dF	Rt_{adj}
Africa	0.20	0.97	0.84	18	0.40
Asia	0.00	0.04	0.98	23	0.31
Europe	0.039	0.010	<0.001	30	0.40
Central America	NA†				
Caribbean	NA				
South America	NA				
North America	NA				
Oceania	NA				

*Adjusted for gross national income per capita (2008) and Human Development Index.
†Not enough (<10) countries with available data.
NA, notavailable.

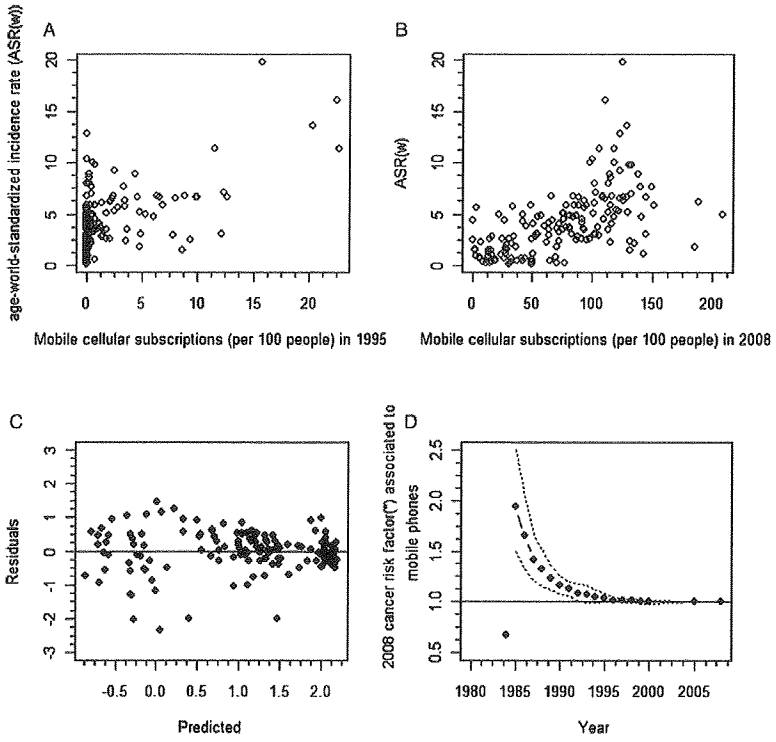


Figure 1 Age-world-standardised incidence rate (ASR(w)) and mobile cellular subscripts (A and B), residuals versus predicted values of the confounder model (C), and risk factors (95% CI) of change in national incidence of cancer of the brain or nervous system in 2008 related to one additional mobile cellular subscription per 100 people in year x (D).

and is likely rather a surrogate for another risk factor.[39] Industry, and more specifically metal,[19] electrical/electronics[40] and textile,[41] has been reported previously. Agriculture has also previously been reported as a risk factor for brain cancer.[42] National electricity consumption and internet usage (broadband and wireless) could be interpreted as indicators of electromagnetic field exposure, although primarily to 50/60 Hz extremely low-frequency.[43] Although speculation, associations with combustible renewables and waste may be associated with biological agents similar to exposures encountered in agriculture.

However, after adjustment for confounding factors these additional potential risk factors that were identified could not be investigated further because of issues of multicollinearity or because not enough data from different countries were available. Lack of data on many risk factors, especially for earlier years, is one of the main limitations of this approach and prohibits more detailed exploration of many risk factors or inclusion of additional confounding factors. This limitation is a general issue for ecological studies using similar data sources. In addition, we highlight the need for consistent collection and collation of such routine data across nations. In the later years of this study, as linkable data became more available, the potential for ecological study increased considerably.

Because of the lack of data from many countries, it was not possible to evaluate non-linearity of the exposure–response associations. This may have contributed to some outliers in the model fit and an underlying heteroscedasticity. If the current trends toward fuller datasets continue then future evaluations of non-linearity and better model fitting may be possible. At present we recommend that linearity is assumed when using such databases to identify potential risk factors, and that properly powered studies with individual-level data be carried out to evaluate non-linearity of exposure–response associations.

Another limitation of the approach described here is the difference in the quality of cancer registration between different countries. For example, incidence data may cover entire national populations but may also, especially in developing countries, cover subnational areas or major cities.[44] It has been reported that in 2006 only about 21% of the world population was actually covered by population-based cancer registries,[45] and only about 8% of the world population by 'good quality' registries (matching CI5 criteria). Sparse registration is most pronounced in Asia (8% of the total population) and Africa (11%),[45] which may in these analyses have resulted in differential impact of residual confounding. Brain cancers (more specifically the incidence of glioma) have indeed been reported to be strongly related to social and economic factors.[46] We aimed to adjust for such differences by adjusting the models for 'Continent', 'Gross National Income in 2008' and 'Human Development Index values', which yielded the best available confounder model explaining about 67% of variation in incidence between countries. However, there may still have been significant residual confounding present. Although we cannot rule this out, we are reassured by the fact that the trend was most notable within Europe where differences in quality of cancer registration are expected to be minimal compared with between-continent differences.

We used weighted age-standardised incidence rates provided by the GLOBOCAN project, and originally based on the methodology outlined by Doll *et al*.[23] As such, we are comparing brain cancer incidence rates as if they were from countries with similar age distributions. Although these require additional assumptions on the age distribution of each country, these have been argued to be most useful for comparing incidence rates over time or between countries since they remove the effects of historical events such as wars and famine.[47] Alternatively, crude

incidence rates were also provided within GLOBOCAN. The differences are relatively small, but nonetheless may have influenced the results.

Ecological studies compared with individual analytic studies are suspect of unavoidable bias.[48] Most notably, 'ecological fallacy' (aggregation bias) indicates that average exposure to a group of people does not, generally, determine their average risk.[49] It has been argued however that in some situations ecological associations can be closer to the true effect than individual-level associations because the latter are themselves also subject to many biases,[50] which may be important in this particular case where mobile phone use was investigated as a risk factor.[51 52] As such, it is important to re-emphasise that ecological studies should not be used to infer causality in a policy context, but the results can, and arguably should, guide further research.

CONCLUSIONS

In conclusion, readily available data may be underused for ecological studies, particularly for exploring risk factors for rare diseases and those with long latency times. These data can, through linkage of different sources, be exploited systematically to explore potential risk factors and to further the exploration of established risk factors for (rare) diseases. We have demonstrated this for cancers of the brain and central nervous system and mobile phone use. In general, the results of ecological studies should not be overinterpreted in causal inference, but equally they should not be ignored where alternative signals of aetiology are lacking.

Acknowledgements The authors would like to thank Dr. Kurt Straif for his insights and discussion on the draft versions of this manuscript.

Contributors FV conceived the study. Study protocol finalised by all authors. FV and KH conducted data collection and statistical analyses. All authors were involved in interpretation of the results. FV wrote the first draft and all authors contributed to subsequent and finals drafts. All authors approved the final version of the manuscript to be published.

Competing interests All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Provenance and peer review Not commissioned; externally peer reviewed.

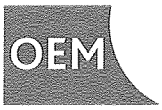
Funding No external funding was obtained for this study.

Data sharing statements The data used in this work are open-access.

REFERENCES

1 Mc Erlean A, Ginsberg MS. Epidemiology of lung cancer. *Semin Roentgenol* 2011;46:173–7.
2 Piantadosi S. Invited commentary: ecological biases. *Am J Epidemiol* 1994;139:761–3.
3 Ferlay J, Shin HR, Bray F, *et al*. *GLOBOCAN 2008 v1.2, cancer incidence and mortality worldwide: IARC cancerbase No. 10*. [Internet]. Lyon, France: International Agency for Research on Cancer, 2010. http://globocan.iarc.fr (accessed 2 Feb 2012).
4 The World Bank. World Bank Development Indicators. http://data.worldbank.org/about (accessed 2 Feb 2012).
5 UNDP. Human Development Reports data. HDI 2010 Index. http://hdr.undp.org/en/media/Lets-Talk-HD-HDI_2010.pdf (accessed 2 Feb 2012).
6 Ostrom QT, Barnholtz-Sloan JS. Current state of our knowledge on brain tumor epidemiology. *Curr Neurol Neurosci Rep* 2011;11:329–35.
7 Hess KR, Broglio KR, Bondy ML. Adult glioma incidence trends in the United States, 1977–2000. *Cancer* 2004;101:2293–9.
8 Kaneko S, Normura K, Yoshimura T, *et al*. Trend of brain tumor incidence by histological subtypes in Japan: estimation from the Brain Tumor Registry of Japan, 1973–1993. *J Neurooncol* 2002;60:61–9.
9 De Vocht F, Burstyn I, Cherrie JW. Time trends (1998–2007) in brain cancer incidence rates in relation to mobile phone use in England. *Bioelectromagnetics* 2011;32:334–9.
10 Deltour I, Johansen C, Auvinen A, *et al*. Time trends in brain tumor incidence rates in Denmark, Finland, Norway, and Sweden, 1974–2003. *J Natl Cancer Inst* 2009;101:1721–4.
11 Desmeules M, Mikkelsen T, Mao Y. Increasing incidence of primary malignant brain tumors: influence of diagnostic methods. *J Natl Cancer Inst* 1992;84:442–5.
12 Polendak AP. Interpretation of secular increases in incidence rates for primary brain cancer in Connecticut adults, 1965–1988. *Neuroepidemiology* 1996;15:51–6.
13 Bondy ML, Scheurer ME, Malmer B, *et al*. Brain tumor epidemiology: consensus from the brain tumor epidemiology consortium. *Cancer* 2008;113(Suppl 7):1953–68.
14 Bohnen NI, Kurland LT. Brain tumor and exposure to pesticides in humans: a review of the epidemiological data. *J Neurol Sci* 1995;132:110–21.
15 Lee WJ, Colt JS, Heinema EF, *et al*. Agricultural pesticide use and risk of glioma in Nebraska, United States. *Occup Environ Med* 2005;62:786–92.
16 Schlehofer B, Hetttinger I, Ryan P, *et al*. Occupational risk factors for low and high grade glioma: results from an international case control study of adult brain tumours. *Int J Cancer* 2005;113:116–25.
17 Buffler PA, Kelsh M, Chapman P, *et al*. Primary brain tumor mortality at a petroleum exploration and extraction research facility. *J Occup Environ Med* 2004;46:257–70.
18 Cocco P, Heineman EF, Dosemeci M. Occupational risk factors for cancer of the central nervous system among US women. *Am J Ind Med* 1999;36:70–6.
19 Rodvall Y, Ahlbohm A, Spannare B, *et al*. Glioma and occupational exposure in Sweden, a case-control study. *Occup Environ Med* 1996;53:526–32.
20 Spinelli V, Chinot O, Cabaniols C, *et al*. Occupational and environmental risk factors for brain cancer: a pilot case-control study in France. *Presse Med* 2010;39:e34–44.
21 Schüz J, Lagorio S, Bersani F. Electromagnetic fields and epidemiology: an overview inspired by the fourth course at the International School of Bioelectromagnetics. *Bioelectromagnetics* 2009;30:511–24.
22 Baan R, Grosse Y, Lauby-Secretan B, *et al*. Carcinogenicity of radiofrequency electromagnetic fields. *Lancet Oncol* 2011;12:624–6.
23 Doll R, Payne P, Waterhouse JAH, eds. *Cancer incidence in five continents*. Vol. I. Geneva: Union Internationale Contre le Cancer, 1966.
24 O'Brien RM, Robert M. A caution regarding rules of thumb for variance inflation factors. *Qual Quantity* 2007;41:673–90.
25 Auvinen A, Toivo T, Tokola K. Epidemiological risk assessment of mobile phones and cancer: where can we improve? *Eur J Cancer Prev* 2006;15:516–23.
26 Lehrer S, Green S, Stock RG. Association between number of cell phone contracts and brain tumor incidence in nineteen U.S. States. *J Neurooncol* 2011;101:505–7.
27 Hardell L, Carlberg M, Hansson Mild K. Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects. *Int J Oncol* 2011;38:1465–74.
28 Schüz J, Steding-Jessen M, Hansen S, *et al*. Long-term mobile phone use and the risk of vestibular schwannoma: a Danish nationwide cohort study. *Am J Epidemiol* 2011;174:416–22.
29 INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case–control study. *Int J Epidemiol* 2010;39:675–94.
30 Larjavaara S, Schüz J, Swerdlow A, *et al*. Location of gliomas in relation to mobile telephone use: a case-case and case-specular analysis. *Am J Epidemiol* 2011;174:2–11.
31 Aydin D, Feychting M, Schüz J, *et al*. Impact of random and systematic recall errors and selection bias in case—control studies on mobile phone use and brain tumors in adolescents (CEFALO study). *Bioelectromagnetics* 2006;32:396–407.
32 Peres J. WHO classification sparks debate over cell phone safety. *J Natl Cancer Inst* 2011;103:1146–7.
33 Cardis E, Sadetzki S. Indications of possible brain-tumour risk in mobile-phone studies: should we be concerned? *Occup Environ Med* 2011;68:169–71.
34 Olsen J. The interphone study: brain cancer and beyond. *Bioelectromagnetics* 2011;32:164–7.
35 Nasca PC, Burnett WS, Greenwald P, *et al*. Population density as an indicator of urban-rural differences in cancer incidence, upstate New York, 1968–1972. *Am J Epidemiol* 1980;112:362–75.
36 Bidoli E, Franceschi S, Montella M. Cancer mortality by urbanization and proximity to the sea coast in Campania Region, southern Italy. *Tumori* 1998;84:460–6.
37 Yang CY, Hsieh YL. The relationship between population density and cancer mortality in Taiwan. *Jpn J Cancer Res* 1998;89:355–60.
38 Schouten LJ, Meijer H, Huveneers JA, *et al*. Urban-rural differences in cancer incidence in The Netherlands 1989–1991. *Int J Epidemiol* 1996;25:729–36.
39 Monroe AC, Ricketts TC, Savitz LA. Cancer in rural versus urban populations: a review. *J Rural Health* 1992;8:212–20.
40 Kheifets L. Electric and magnetic field exposure and brain cancer: a review. *Bioelectromagnetics* 2001;22(Suppl 5):S120–31.
41 Heineman EF, Gao YT, Dosemeci M, *et al*. Occupational risk factors for brain tumors among women in Shanghai, China. *J Occup Environ Med* 1995;37:288–93.

42 Khuder SA, Mutgi AB, Schaub EA. Meta-analyses of brain cancer and farming. *Am J Ind Med* 1998;34:252–60.
43 Kheifets L, Ahlbom A, Crespi CM, *et al*. A pooled analysis of extremely low-frequency magnetic fields and childhood brain tumors. *Am J Epidemiol.* 2010;172:752–61.
44 Ferlay J, Shin HR, Bray F, *et al*. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
45 Parkin DM. The evolution of the population-based cancer registry. *Nat Rev Cancer* 2006;6:603–12.
46 Clouston SAP. Social and economic patterning in the Interphone study. *Int J Epidemiol* 2011;40:1122.
47 Ahmad OB, Boschi-Pinto C, Lopex AD, *et al*. Age standardization of rates: A new WHO standard. GPE Discussion paper series: Mo.31. EIP/GPE.EDB World Health Organization. 2001. http://www.who.int/healthinfo/paper31.pdf (accessed 23 Aug 2012).
48 Greenland S, Morgenstern H. Ecological bias, confounding, and effect modification. *Int J Epidemiol* 1989;18:269–74.
49 Robinson WS. Ecological correlations and the behaviour of individuals. *Am Sociol Rev* 1950;15:351–7.
50 Greenland S, Robins J. Accepting the limits of ecological studies: Drs. Greenland and Robins reply to Drs. Piantadosi and Cohen. *Am J Epidemiol* 1994;139:769–71.
51 Vrijheid M, Armstrong BK, Bédard D, *et al*. Recall bias in the assessment of exposure to mobile phones. *J Expo Sci Environ Epidemiol* 2009;19:369–81.
52 Aydin D, Feychting M, Schüz J, *et al*. Mobile phone use and brain tumors in children and adolescents: a multicenter case-control study. *J Natl Cancer Inst* 2011;103:1264–76.



Environmental risk factors for cancers of the brain and nervous system: the use of ecological data to generate hypotheses

Frank de Vocht, Kimberly Hannam and Iain Buchan

Occup Environ Med 2013 70: 349-356 originally published online January 23, 2013
doi: 10.1136/oemed-2012-100954