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L. HARDELL, N. CARLBERG, F. SEDERQVIST, K.H. MILD
Meta-analysis of long-term mobile phone use and the association with brain tumours
Internat J Oncology 2008 12 : 1097-1103. http://oem.bmj.com/content/64/9/626.full and http://www.mast-victims.org/resources/docs/hardell-meta-analysis-2008.pdf .

And related articles by **L. HARDELL et als.**:
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Methodological Aspects of Epidemiological Studies on the Use of Mobile Phones and their Association with Brain Tumors. Open Environmental Sciences, 2008, 2, 54-61 54 1876-3251/08 2008 http://www.benthamscience.com/open/toenvirj/articles/V002/54TOENVIRSJ.pdf
Mobile telephones and cancer: Is there really no evidence of an association? (Review). Intl. J. Mol Med. 12: 67-72, 2003 http://www.avaate.org/IMG/pdf/Int_J_Mol_Med_2003_12_67.pdf

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Meta-analysis of long-term mobile phone use and the association with brain tumours

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Abstract. We evaluated long-term use of mobile phones and the risk for brain tumours in case-control studies published so far on this issue. We identified ten studies on glioma and meta-analysis yielded OR = 0.9, 95% CI = 0.8-1.1. Latency period of ≥10-years gave OR = 1.2, 95% CI = 0.8-1.9 based on six studies, for ipsilateral use (same side as tumour) OR = 2.0, 95% CI = 1.2-3.4 (four studies), but contralateral use did not increase the risk significantly, OR = 1.1, 95% CI = 0.6-2.0. Meta-analysis of nine studies on acoustic neuroma gave OR = 0.9, 95% CI = 0.7-1.1 increasing to OR = 1.3, 95% CI = 0.6-2.8 using ≥10-years latency period (four studies). Ipsilateral use gave OR = 2.4, 95% CI = 1.1-5.3 and contralateral OR = 1.2, 95% CI = 0.7-2.2 in the ≥10-years latency period group (three studies). Seven studies gave results for meningioma yielding overall OR = 0.8, 95% CI = 0.7-0.99. Using ≥10-years latency period OR = 1.3, 95% CI = 0.9-1.8 was calculated (four studies) increasing to OR = 1.7, 95% CI = 0.99-3.1 for ipsilateral use and OR = 1.0, 95% CI = 0.3-3.1 for contralateral use (two studies). We conclude that this meta-analysis gave a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using ≥10-years latency period.

Introduction

Worldwide there has been a rapid development of wireless technology and along with that an increased use of wireless telephone communication during the last decade. Everyone is exposed to radiofrequency/microwave (RF) radiation emissions from wireless devices such as cellular phones and cordless phones, cellular antennas and towers, broadcast transmission towers, voice and data transmission for cell phones, pagers and personal digital assistants (PDAs) and other sources of RF radiation. This has raised concern of health risks, primarily an increased risk for brain tumours since the brain is the target organ for microwave exposure during mobile phone calls.

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Since Sweden was one of the first countries in the world to adopt this wireless technology a brief history is given in the following. First, analogue phones (NMT; Nordic Mobile Telephone System) were introduced on the market in the early 1980's using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden since 1981 but closed down in December 31, 2007, whereas 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 now dominates the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900 MHz RF fields has been introduced worldwide since a few years, in Sweden in 2003.

Desktop cordless phones (DECT) started in 1988 using first analogue 800-900 MHz RF fields, but since early 1990's the digital 1,900 MHz system. In our studies on tumour risk associated with use of wireless phones we have also assessed use of DECT. However, most other research groups have not published such data or only in a scanty way, so exposure to RF from DECT is not further discussed here. Instead the reader is referred to our publications with the results as published previously (1-3).

The initial studies on brain tumour risk had too short latency periods to give a meaningful interpretation of long-term risk. However, during recent years studies have been published that enable evaluation of ≥10-years latency period risk, although still mostly based on low numbers (4,5). A ≥10-years latency period seems to be a reasonable minimum period to indicate long-term carcinogenic risks from exposure to RF fields during use of cellular or cordless phones.

Long-term exposure to RF fields from mobile phones and brain tumour risk is of importance to evaluate not the least since the use of cellular phones is globally widespread with high prevalence among almost all age groups in the population.

Materials and methods

In addition to our constant gathering of new studies in this area we used the Pub Med database (www.ncbi.nlm.nih.gov) for search of all relevant studies. We used mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. If a study had several publications on certain aspects we used the latest publication giving the most relevant data.

Table I. Odds ratios (ORs) and 95% confidence intervals (CIs) from 10 case-control studies on glioma including meta-analysis of the studies.[a]

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip *et al* 2001, USA (12)	201	358	1.0	0.7-1.4
Auvinen *et al* 2002, Finland (13)	Not given	Not given	1.5	1.0-2.4
Lönn *et al* 2005, Sweden (14)	214	399	0.8	0.6-1.0
Christensen *et al* 2005, low-grade glioma, Denmark (15)	47	90	1.1	0.6-2.0
Christensen *et al* 2005, high-grade glioma, Denmark (15)	59	155	0.6	0.4-0.9
Hepworth *et al* 2006, UK (16)	508	898	0.9	0.8-1.1
Schüz *et al* 2006, Germany (17)	138	283	1.0	0.7-1.3
Hardell *et al* 2006, Sweden (1), all glioma	346	900	1.4	1.1-1.7
Low-grade glioma	65	900	1.4	0.9-2.3
High-grade glioma	281	900	1.4	1.1-1.8
Lahkola *et al* 2006, Denmark, Norway, Finland, Sweden, UK (18)	867	1,853	0.8	0.7-0.9
Hours *et al* 2007, France (19)	59	54	1.2	0.7-2.1
Klaeboe *et al* 2007, Norway (20)	161	227	0.6	0.4-0.9
Meta-analysis	Not given[b]	Not given[b]	0.9	0.8-1.1

[a]Numbers of exposed cases and controls are given. [b]Total number could not be calculated since numbers were not presented in one publication (13).

Brain tumours include both malignant and benign types. Thus, it is worthwhile to give results for different types and in the following we discuss glioma, acoustic neuroma and meningioma, the major tumour types, separately. Compared with our previous publications (4,5) we have now up-dated the number of included studies and made some further analysis. For details about the studies the reader is referred to our previous reviews and the original studies. We give overall results as well as ≥10-years latency period results and, if presented, ipsilateral use of the cellular phones, i.e. same side of tumour and microwave exposure, and contralateral (opposite side) use. If the study did not have users with a ≥10-year latency period only the overall results are presented.

Statistical methods. For statistical analysis Stata 8.2 was used (Stata/SE 8.2 for Windows; StataCorp., College Station TX). Random effects model was used for all meta-analysis, to allow for between-study statistical heterogeneity. The analyses were based on the adjusted ORs in the different studies. In our studies (1,2) the unexposed group consisted of cases and controls with no reported use of either mobile or cordless phones. On the contrary almost all other studies did not assess use of cordless phones, and cases and controls with such use were included in the 'unexposed' group when mobile phone use was analyzed.

Results

We identified two publications from a cohort study of mobile phone users (6,7) and 19 case-control studies on this topic (1,2,8-25; note refs. 8 and 9 are the same study). Two publications (18,23) overlapped partly already published studies, but were included since also new results were presented in these publications. No mortality studies were included.

The Danish cohort study with two publications (6,7) had several limitations, such as exclusion of the heaviest mobile phone users, no truly unexposed comparison group, skewed sex distribution and no data were given on laterality of phone use in relation to tumour localisation in the brain. This study was uninformative regarding long-term health effects from mobile phone use, as has been discussed elsewhere (4). Furthermore, this was a cohort study that gave standardised incidence rates and not odds ratios (OR) and 95% confidence intervals (CI) as in the case-control studies. For these reasons this cohort study was excluded from this review.

Two case-control studies were excluded since results were not presented separately for glioma, acoustic neuroma and meningioma (8-10). Our first study on this topic was the first one to indicate an association between use of mobile phones and ipsilateral brain tumours, although based on low numbers (8,9). In one case-control study on acoustic neuroma overall results were not presented, only for some time periods without data for ≥10-years latency period, and it was thus excluded from this review (11). The following presentation was based on results from 16 case-control studies.

Glioma. Ten case-control studies gave results for glioma risk associated with the use of mobile phones (1,12-20). Seven of these studies (14-20) were part of the Interphone study on this issue, and one of these (18) overlapped partly three of other Interphone studies (14-16) but included also results for Finland (Table I). Later also results form Norway have been published separately (20). It should be noted that in one study the group of glioma cases was heterogenic including also ependymoma, i.e., a benign tumour, but probably few subjects

Table II. Odds ratios (ORs) and 95% confidence intervals (CIs) from 6 case-control studies on glioma including meta-analysis of the studies using ≥10 years latency period.[a]

Study Author, year of publication, country, latency, refs. no.	Total			Ipsilateral			Contralateral		
	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn *et al* 2005, Sweden, ≥10 years (14)	25/38	0.9	0.5-1.5	15/18	1.6	0.8-3.4	11/25	0.7	0.3-1.5
Christensen *et al* 2005, Denmark, low-grade glioma, ≥10 years (15)	6/9	1.6	0.4-6.1	-	-	-	-	-	-
Christensen *et al* 2005, Denmark, high-grade glioma, ≥10 years (15)	8/22	0.5	0.2-1.3	-	-	-	-	-	-
Hepworth *et al* 2006, UK, >10 years (16)	66/112	0.9	0.6-1.3	Not given[b]	1.6	0.9-2.8	Not given[b]	0.8	0.4-1.4
Schüz *et al* 2006, Germany, ≥10 years (17)	12/11	2.2	0.9-5.1	-	-	-	-	-	-
Hardell *et al* 2006, Sweden, >10 years (1), all glioma	78/99	2.7	1.8-3.9	41/28	4.4	2.5-7.6	26/29	2.8	1.5-5.1
Low-grade glioma	7/99	1.5	0.6-3.8	2/28	1.2	0.3-5.8	4/29	2.1	0.6-7.6
High-grade glioma	71/99	3.1	2.0-4.6	39/28	5.4	3.0-9.6	22/29	3.1	1.6-5.9
Lahkola *et al* 2006, Denmark, Norway, Finland, Sweden, UK, ≥10 years (18)	143/220	0.95	0.7-1.2	77/117	1.4	1.01-1.9	67/121	1.0	0.7-1.4
Meta-analysis	338/511	1.2	0.8-1.9	Not given[b]	2.0	1.2-3.4	Not given[b]	1.1	0.6-2.0

[a]Numbers of exposed cases and controls are given. [b]Total number could not be calculated since numbers were not presented in one publication (16).

(13). The risk was significantly decreased in the Danish part (15) for high-grade glioma with OR = 0.6, 95% CI = 0.4-0.9, for all glioma in the study in Norway (20) with OR = 0.6, 95% CI = 0.4-0.9, and the Finnish publication (18) with OR = 0.8, 95% CI = 0.7-0.9. In the Swedish part of Interphone studies decreased OR of borderline significance was presented (14). In a register based case-control study from Finland (13), that was not part of the Interphone study, an increased OR = 1.5 of borderline significance was reported (95% CI = 1.0-2.4). In our Swedish study (1), independent from Interphone, OR = 1.4, 95% CI = 1.1-1.7 was reported for all glioma. Meta-analysis of the 10 case-control studies yielded OR = 0.9, 95% CI = 0.8-1.1.

In Table II results are presented for the six studies (1,14-18) that gave results for a latency period of at least 10 years. Most of the results in the various studies were based on low numbers. Meta-analysis gave OR = 1.2, 95% CI = 0.8-1.9. In four case-control studies results for ipsilateral use of a mobile phone were presented (1,14,16,18). All showed increased OR and meta-analysis yielded OR = 2.0, 95% CI = 1.2-3.4. However, contralateral use did not increase the risk significantly, OR = 1.1, 95% CI = 0.6-2.0.

Acoustic neuroma. Regarding acoustic neuroma nine case-control studies have been published, Table III (2,12,19-25). Seven of these were part of the Interphone studies (19-25). One of these (23) overlapped partly two other Interphone studies (21,22) and one published later (20). One of the largest studies came from Sweden and was not part of the Interphone studies (2). It gave significantly increased OR = 1.7, 95% CI = 1.2-2.3. Six of the seven Interphone studies reported somewhat decreased ORs, although not significantly so. Meta-analysis gave OR = 0.9, 95% CI = 0.7-1.1.

Results for a latency period of 10 years or more were reported in four (2,21-23) of these nine studies (Table IV). Again, using this latency period most of the results were based on low numbers. In total, meta-analysis gave OR = 1.3, 95% CI = 0.6-2.8, whereas for ipsilateral use of the mobile phone OR increased to 2.4, 95% CI = 1.1-5.3, based on three studies. Contralateral use yielded OR = 1.2, 95% CI = 0.7-2.2.

Meningioma. For meningioma results have been published from seven case-control studies, Table V (2,12,14,15,17,19,20). Of these, five (14,15,17,19,20) were part of the Interphone study and all gave decreased OR for meningioma, significantly

Table III. Odds ratios (ORs) and 95% confidence intervals (CIs) from 9 case-control studies on acoustic neuroma including meta-analysis of the studies.[a]

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip *et al* 2001, USA (12)	40	358	0.8	0.5-1.4
Lönn *et al* 2004, Sweden (21)	89	356	1.0	0.6-1.5
Christensen *et al* 2004, Denmark (22)	45	97	0.9	0.5-1.6
Schoemaker *et al* 2005, Denmark, Finland, Sweden, Norway, Scotland, UK (23)	360	1,934	0.9	0.7-1.1
Hardell *et al* 2006, Sweden (2)	130	900	1.7	1.2-2.3
Takebayashi *et al* 2006, Japan (24)	51	192	0.7	0.4-1.2
Klaeboe *et al* 2007, Norway (20)	22	227	0.5	0.2-1.0
Schlehofer *et al* 2007, Germany (25)	29	74	0.7	0.4-1.2
Hours *et al* 2007, France (19)	58	123	0.9	0.5-1.6
Meta-analysis	824	4,261	0.9	0.7-1.1

[a]Numbers of exposed cases and controls are given.

Table IV. Odds ratios (ORs) and 95% confidence intervals (CIs) from 4 case-control studies on acoustic neuroma including meta-analysis of the studies using ≥10 years latency period.[a]

	Total			Ipsilateral			Contralateral		
Study Author, year of publication, country, latency, refs. no.	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn *et al* 2004, Sweden, ≥10 years (21)	14/29	1.8	0.8-4.3	12/15	3.9	1.6-9.5	4/17	0.8	0.2-2.9
Christensen *et al* 2004, Denmark, ≥10 years (22)	2/15	0.2	0.04-1.1	-	-	-	-	-	-
Schoemaker *et al* 2005, Denmark, Finland, Sweden, Norway, Scotland, UK, ≥10 years (23)	47/212	1.0	0.7-1.5	31/124	1.3	0.8-2.0	20/105	1.0	0.6-1.7
Hardell *et al* 2006, Sweden, >10 years (2)	20/99	2.9	1.6-5.5	10/28	3.5	1.5-7.8	6/29	2.4	0.9-6.3
Meta-analysis	83/355	1.3	0.6-2.8	53/167	2.4	1.1-5.3	30/151	1.2	0.7-2.2

[a]Numbers of exposed cases and controls are given.

so in the Swedish part with OR = 0.7, 95% CI = 0.5-0.9 (14). The largest study was a Swedish investigation independent from Interphone based on 347 exposed cases. It gave OR = 1.1, 95% CI = 0.9-1.3. Meta-analysis gave significantly decreased risk with OR = 0.8, 95% CI = 0.7-0.99.

Four case-control studies remained for the analysis of a 10-years latency period, Table VI (2,14,15,17). In total no study showed significantly increased OR and meta-analysis gave OR = 1.3, 95% CI = 0.9-1.8. The analysis of ipsilateral microwave exposure was based on two studies and the meta-analysis gave OR = 1.7, 95% CI = 0.99-3.1. Regarding contralateral exposure no increased risk was found, OR = 1.0, 95% CI = 0.3-3.1.

Discussion

Different biological effects have been reported from exposure to radiofrequency/microwave fields, for an overview see two recent reports (5,26). Of special concern is the risk for brain tumours due to the high near field exposure to the brain during mobile phone calls compared with other sources of RF fields. In total 19 case-control studies have been performed

Table V. Odds ratios (ORs) and 95% confidence intervals (CIs) from 7 case-control studies on meningioma including meta-analysis of the studies.[a]

Study Author, year of publication, country, ref. no.	No. of cases	No. of controls	OR	95% CI
Inskip *et al* 2001 (USA) (12)	67	358	0.8	0.5-1.2
Lönn *et al* 2005 (Sweden) (14)	118	399	0.7	0.5-0.9
Christensen *et al* 2005 (Denmark) (15)	67	133	0.8	0.5-1.3
Schüz *et al* 2006 (Germany) (17)	104	234	0.8	0.6-1.1
Hardell *et al* 2006 (Sweden) (2)	347	900	1.1	0.9-1.3
Klaeboe *et al* 2007 (Norway) (20)	96	227	0.8	0.5-1.1
Hours *et al* 2007 (France) (19)	71	80	0.7	0.4-1.3
Meta-analysis	870	2,331	0.8	0.7-0.99

[a]Numbers of exposed cases and controls are given.

Table VI. Odds ratios (ORs) and 95% confidence intervals (CIs) from 4 case-control studies on meningioma including meta-analysis of the studies using ≥10 years latency period.[a]

	Total			Ipsilateral			Contralateral		
Study Author, year of publication, country, latency, refs. no.	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI	No. of cases/ controls	OR	95% CI
Lönn *et al* 2005, Sweden, ≥10 years (14)	12/36	0.9	0.4-1.9	5/18	1.3	0.5-3.9	3/23	0.5	0.1-1.7
Christensen *et al* 2005, Denmark, ≥10 years (15)	6/8	1.0	0.3-3.2	-	-	-	-	-	-
Schüz *et al* 2006, Germany, ≥10 years (17)	5/9	1.1	0.4-3.4	-	-	-	-	-	-
Hardell *et al* 2006, Sweden, ≥10 years (2)	38/99	1.5	0.98-2.4	15/28	2.0	0.98-3.9	12/29	1.6	0.7-3.3
Meta-analysis	61/152	1.3	0.9-1.8	20/46	1.7	0.99-3.1	15/52	1.0	0.3-3.1

[a]Numbers of exposed cases and controls are given.

on that topic, but since few subjects have used the mobile phone for at least 10 years conclusions on long-term effects have been hampered. By now a number of studies exist with such data, so presentation of the results in the various studies is meaningful as well as meta-analysis of the data.

As to carcinogenesis usually latency period of at least 10 years is needed for more firm conclusions. For several carcinogens such as smoking and asbestos exposure and the risk for lung cancer, dioxins and certain cancer types even longer latency periods may be required (27,28). Thus, it is premature to draw conclusions on the association between mobile phones and brain tumours based on short latency period, as has been the situation in some commentaries (29).

This review included 19 case-control studies. Two publications from a Danish cohort study on mobile phone users (6,7) were excluded due to limitations in the study design, as discussed above. Our first study on this topic was excluded, since analysis was not performed for different histology types (8,9). This was one of the first studies in this area and the first to indicate an association between mobile phone use and ipsilateral brain tumours. Two studies from USA were excluded for the same reason as our first one or because overall data were not presented (10,11). However, in that study mobile phone use during 3-6 years, that was the longest observation time, gave OR = 1.7, 95% CI = 0.5-5.1 based on 11 cases and 6 controls (11).

It should be noted that several of the overall ORs in the Interphone studies were <1.0, some even significantly so. As an example, in the Danish Interphone study on glioma (15) all 17 ORs for high-grade glioma were <1.0, four significantly decreased. In the Swedish Interphone study on glioma 46 ORs were presented with overall results (14). Of these ORs 45 were <1.0, six even signficantly so. On the contrary, regarding glioma using a latency period of ≥10 years increased ORs for ipsilateral exposure were found in all Interphone studies that present such data, see Table II. The overall decreased risks would thus bias the 10-years latency period calculations towards unity. These results in the Interphone

studies give concern about the methods used, such as assessment and interpretation of exposure and statistical analysis.

For biological reasons it is not believed that microwave exposure from mobile phones do prevent brain tumours, as indicated in some results in the Interphone studies. Thus, the design and performance of these studies, using the same core protocol, seem to be biased in certain respects. This has been discussed by others and us elsewhere (4,5,30,31). In a Danish Interphone study it was concluded that the cognitive function in brain tumour cases was affected leading to e.g. deficient memory (15). Patients scored significantly lower than controls with problems to recall words (aphasia), writing and drawing due to paralysis.

Also the interviewing of cases in such short time after diagnosis in the Interphone studies, even bedside (e.g. 17), might have biased assessment of exposure due to a stressful situation for the patient with memory and other defects of the cognitive functions. It should further be noted that some of the Interphone studies had very low response rates with the possibility of selection bias. In the publication on mobile phone use and risk of glioma in five North European countries 37-81% (total 60%) of the cases and 42-69% (total 50%) of the controls participated (18). This is to be compared with the response rates in our studies (1,2). Of cases with malignant brain tumours 905 (90%) answered the questionnaire. The corresponding results were for cases with benign brain tumours 1,254 (88%) and controls 2,162 (89%).

In addition to selection bias of cases and controls in the Interphone studies, recall bias due to e.g. cognitive defects in the patients might have been introduced. Computer guided face-to-face interviews of cases at the hospitals shortly after operation may have been a contributing factor. We used postal questionnaires both for cases and controls. The cases could answer the questionnaire some time after the operation, usually about two months later. If necessary, the answers were supplemented over the phone. All assessment of exposure and coding of data in our studies were blinded as to case or control status. On the contrary, face-to-face interviews of both cases and controls in the Interphone studies might have introduced observational bias since it was known if it was a patient or a referent that was interviewed.

Some articles have discussed methodological issues in the Interphone studies (30,31). The actual use of mobile phones was underestimated in light users and overestimated in heavy users. Random recall bias could lead to large underestimation in the risk of brain tumours associated with mobile phone use. It was further suggested that selection bias in the Interphone study resulted in under selection of unexposed controls with decreasing risk at low to moderate exposure levels.

Furthermore, it should be added that in our studies we also assessed use of cordless phones (1,2). The unexposed group consisted of cases and controls with no use of mobile or cordless phones. In contrast, e.g. the Interphone studies did not assess use of cordless phones or did not report any details (14,17). Such use seems to have been included in the unexposed group in the statistical analysis of an association between mobile phone use and brain tumours. We found increased OR for glioma and acoustic neuroma associated with use of both mobile and cordless phones, whereas overall OR was not significantly increased for meningioma (1,2). It has been shown that the GSM phones have a median power in the same order of magnitude as cordless phones (32). Moreover, cordless phones are usually used for longer calls than mobile phones (1,2). Including subjects using cordless phones in the 'unexposed' group in studies on this issue, as for example in the Interphone investigations, would thus underestimate the risk.

We report here results from ten case-control studies on glioma. No association was found with mobile phone use in the overall meta-analysis. However, using a ≥10-years latency period showed increased OR in the four studies with data on ipsilateral use of the mobile phone, significantly so in the meta-analysis. Contralateral use yielded OR close to unity. These findings are most likely of biological relevance taking into account both a reasonable latency period and tumour localisation in relation to microwave exposure and should therefore be considered in relation to carcinogenesis (33,34).

Since one publication on glioma (18) partly overlapped three other Interphone studies (14-16) we excluded them in one analysis. Later also results from Norway have been published but without any 10-years latency period data (20). Using ≥10-years latency period yielded OR = 1.7, 95% CI = 0.8-3.9, ipsilateral exposure OR = 2.4, 95% CI = 0.8-7.4 and contralateral exposure OR = 1.6, 95% CI = 0.6-4.4.

Also regarding acoustic neuroma ipsilateral exposure to microwaves yielded increased OR in the three studies with such data, significantly so in the meta-analysis. Contralateral exposure did not give significantly increased OR. These findings are similar as for glioma. Since one of the Interphone publications (23) partly overlapped two other (21,22) with 10-years latency data we excluded these two studies in one analysis. Using ≥10-years latency period yielded OR = 1.7, 95% CI = 0.6-4.7, ipsilateral exposure OR = 2.0, 95% CI = 0.8-5.3 and contralateral exposure OR = 1.4, 95% CI = 0.6-3.2.

Results on meningioma for ≥10 years latency period were presented in four studies and ipsilateral exposure in two investigations. Thus, these results were based on lower numbers than for glioma or acoustic neuroma. No significant association was found although ipsilateral exposure gave OR = 1.7 with 95% CI 0.99-3.1.

It might be discussed if the results would be changed if our studies (1,2) were excluded from the meta-analysis. Regarding glioma this yielded for ≥10-years latency period overall OR = 1.0, 95% CI = 0.8-1.2, ipsilateral exposure OR = 1.5, 95% CI = 1.1-1.9 and contralateral exposure OR = 0.9, 95% CI = 0.7-1.2. For acoustic neuroma the corresponding results gave overall OR = 0.9, 95% CI = 0.4-2.0, ipsilateral exposure OR = 2.1, 95% CI = 0.7-6.1 and contralateral exposure OR = 1.0, 95% CI = 0.6-1.6. Regarding meningioma overall OR was 1.0, 95% CI = 0.6-1.6. Only one study (14) remained for calculations of ipsilateral and contralateral exposure (Table VI).

As shown above an association was still found between mobile phone use and ipsilateral glioma and acoustic neuroma, significantly so for glioma, even if our studies (1,2) were excluded. Another meta-analysis that did not include our studies found a significant association between mobile phone use and all brain tumours using ≥10 years latency

period with OR = 1.25, 95% CI = 1.01-1.54 (35). One more meta-analysis was performed on mobile phone use yielding for contralateral brain tumours OR = 1.0, 95% CI = 0.8-1.4 and for ipsilateral brain tumours OR = 1.3, 95% CI = 0.99-1.9. No analysis was performed for ≥10 year latency time (36).

In conclusion this meta-analysis gave a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using ≥10-years latency period. No association was found for contralateral tumours. These results are most likely of biological relevance and further strengthen the hypothesis of a carcinogenic effect from microwave emissions from mobile phones.

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Mobile phones, cordless phones and the risk for brain tumours

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Abstract. The Hardell-group conducted during 1997-2003 two case control studies on brain tumours including assessment of use of mobile phones and cordless phones. The questionnaire was answered by 905 (90%) cases with malignant brain tumours, 1,254 (88%) cases with benign tumours and 2,162 (89%) population-based controls. Cases were reported from the Swedish Cancer Registries. Anatomical area in the brain for the tumour was assessed and related to side of the head used for both types of wireless phones. In the current analysis we defined ipsilateral use (same side as the tumour) as ≥50% of the use and contralateral use (opposite side) as <50% of the calling time. We report now further results for use of mobile and cordless phones. Regarding astrocytoma we found highest risk for ipsilateral mobile phone use in the >10 year latency group, OR=3.3, 95% CI=2.0-5.4 and for cordless phone use OR=5.0, 95% CI=2.3-11. In total, the risk was highest for cases with first use <20 years age, for mobile phone OR=5.2, 95% CI=2.2-12 and for cordless phone OR=4.4, 95% CI=1.9-10. For acoustic neuroma, the highest OR was found for ipsilateral use and >10 year latency, for mobile phone OR=3.0, 95% CI=1.4-6.2 and cordless phone OR=2.3, 95% CI=0.6-8.8. Overall highest OR for mobile phone use was found in subjects with first use at age <20 years, OR=5.0, 95% CI 1.5-16 whereas no association was found for cordless phone in that group, but based on only one exposed case. The annual age-adjusted incidence of astrocytoma for the age group >19 years increased significantly by +2.16%, 95% CI +0.25 to +4.10 during 2000-2007 in Sweden in spite of seemingly underreporting of cases to the Swedish Cancer Registry. A decreasing incidence was found for acoustic neuroma during the same period. However, the medical diagnosis and treatment of this tumour type has changed during recent years and underreporting from a single center would have a large impact for such a rare tumour.

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Introduction

During the last decade there was a rapid increase in the use of wireless phones and the prevalence has reached 100% in many countries. Concerns about different health risks have been raised, particularly an increased risk for brain tumours (1). The ipsilateral brain (same side as the mobile phone has predominantly been used) is most exposed, whereas the contralateral side (opposite side to the mobile phone) is much less exposed (2). It is thus of vital importance to have information on the localisation of the tumour in the brain and which side of the head that has predominantly been used during phone calls.

Studies in this area have been hampered by rather short latencies for the different types of wireless phones. In general carcinogenesis usually takes decades from first exposure to manifest cancer, although shorter latencies have been implicated for promoters and certain types of diseases, e.g. ionising radiation and leukemia (3-5). Sweden was one of the first countries in the world to adopt this new technology so studies with longer latencies are possible and health effects from the wireless technology may be especially pertinent in our country for early warnings. Analogue phones (NMT, Nordic Mobile Telephone System) were introduced on the market in the early 1980s using both 450 and 900 Megahertz (MHz) fields. NMT 450 was used in Sweden beginning in 1981 and ending in December 31, 2007, whereas NMT 900 operated from 1986 to 2000.

The market is now dominated by the digital system (GSM, Global System for Mobile Communication) that started in 1991 and uses dual band, 900 and 1,800 MHz. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900 MHz RF fields has been introduced around the world more recently, in Sweden since 2003. The desktop cordless phones (Digital Enhanced Cordless Telecommunication, cordless phone) have been used in Sweden since 1988, first analogue 800-900 MHz RF fields, but since early 1990s the digital 1,900 MHz system has been used.

Results from the Hardell-group have been published previously on the association between use of mobile or cordless phones and brain tumours. All studies were approved by the local Ethics Committee. These studies are briefly discussed in the following and additional results are presented on e.g. age-dependent brain tumour risk. The aim of this presentation is not to give a review of this area, since such publications can be found elsewhere (6,7). In addition to our studies only a few publications from the so-called Interphone group give results

for 10-year latency (7). That group includes 13 countries and cases and controls were recruited during 1999-2004, varying for different countries. For unclear reasons the final results have not yet been published.

In 1999 we published results from our first case control study on brain tumours and use of mobile phones (8). In total 209 (90%) of the cases and 425 (91%) of the controls that fullfilled the inclusion criteria answered the mailed questionnaire. Overall we did not find an association. For ipsilateral exposure we saw a somewhat increased risk (9). These results were based on low numbers of exposed subjects and short latency periods, so no firm conclusions could be drawn. Furthermore, in this first study we did not include the use of cordless phone.

This initial study was followed by two larger studies by us on the same topic. The aim of this paper was to report results from further analyses of these large studies, as will be presented below.

The second case control study included cases diagnosed during the time period January 1, 1997 through June 30, 2000 and population-based controls. All cases were reported to a cancer registry and had histopathological verfication of tumour diagnosis. The study included the use of cordless phones, as well as asking more questions on e.g. occupational exposures. Use of wireless phones was carefully assessed by a self-administered questionnaire. The information was supplemented over the phone, if necessary. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions; >50% of the time for one side, or equally both sides. This information was checked during the supplementary phone call. Moreover, every person that had used a mobile phone received after that a letter asking them again to specify the ear that had been used during phone calls and to what extent that side of the head was mostly used, e.g. 100, 70 and 50% etc. There was a very good agreement for the result using these three methods to assess these data.

Separately, tumour localisation was defined by using medical records, such as computer tomography (CT) and/or magnetic resonance imaging (MRI). After that use of the wireless phone was defined as ipsilateral (>50% of the time), equally ipsi/contralateral or contralateral (<50%) in relation to tumour side. The tumour type was defined by using histopathology studies. In the calculation of cumulative hours of use over the years we used information of first and last year for use (time period) and average number of minutes per day during that period. Use in a car with external antenna was disregarded as well as use of a handsfree device. We adopted a minimum latency period of one year. Hence, we could define latency period and cumulative use for the different phone types.

Only living subjects were included in our studies and this second case control study included 1,429 (88%) cases and 1,470 (91%) controls. The results regarding use of wireless phones have been published previously (10-13).

This study was followed by our third case control study on the same topic. The methods were the same as in the second study using an identical questionnaire. The study period was from July 1, 2000 until December 31, 2003. In total 729 (89%) cases and 692 (84%) controls participated, as previously published (14,15).

We made pooled analysis of the two case control studies on brain tumour cases diagnosed 1997-2003, both malignant (16) and benign (17). This was possible since the same methods were used in both studies with an identical questionnaire. For more details about the study design, see our previous publications.

Materials and methods

We have previously reported findings for different age groups at the time of diagnosis in the study with inclusion period 1997-2000 (18). Now we have re-analysed the whole study period 1997-2003, especially in regard to age at the first time for use of a wireless phone and the association with different types of brain tumours. We analysed also type of phone and laterality of tumour according to the method by Inskip *et al* (19). Furthermore, we evaluated the risk for tumour for men and women separately, anatomical localisations in the brain, latency for first use of mobile phone or cordless phone, survival and incidence of brain tumours in Sweden.

We used three age groups for first use of a wireless phone; <20 years, 20-49 years and 50-80 years. For laterality analysis of tumour in relation to phone use one group consisted of ipsilateral and varying ipsi/contralateral use (in the following called ipsilateral), the other of contralateral use. The malignant brain tumours (n=905) were divided into astrocytoma grade I-IV (n=663), oligodendroglioma (n=93), other/mixed glioma (n=78) and other types (medulloblastoma n=6, ependymoma n=19, other types n=46). The benign tumours (n=1,254) were divided into acoustic neuroma (n=243), meningioma (n=916) and other types (n=96). One case had both acoustic neuroma and meningioma and another case had both 'other type' malignant tumour and acoustic neuroma.

Statistical methods. All analyses were done using StataSE 10.1 (Stata/SE 10.1 for Windows; StataCorp., College Station, TX). Odds ratio (OR) and 95% confidence interval (CI) were calculated using unconditional logistic regression analysis. The unexposed category consisted of subjects that reported no use of mobile or cordless phones. Adjustment was made for gender, age (as a continuous variable), socio-economic index (SEI) and year of diagnosis. The same year as for the case was used for the corresponding control. Ipsilateral use of a wireless phone was defined here as ≥50% on the tumour side. Note, that laterality of the tumour was not available for all cases, e.g., midline tumours or tumours in both hemispheres.

Results

Malignant brain tumours. For malignant brain tumours we obtained answers from 905 (90%) cases (16). For reference the whole control population of 2,162 (89%) subjects during 1997-2003 was used.

Different malignant tumour types. Regarding mobile phones OR=1.4, 95% CI=1.1-1-7 was calculated for astrocytoma grade I-IV, increasing to OR 2.0, 95% CI=1.5-2.5 for ipsilateral use, whereas no increased risk was found for contralateral use, Table I. Using >10-year latency time yielded higher ORs and

Table I. Odds ratio (OR) and 95% confidence interval (CI) for astrocytoma grade I-IV (n=663).[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone,	346/900	229/374	98/308
>1 year latency	1.4	2.0	1.0
	1.1-1.7	1.5-2.5	0.7-1.4
>10 year latency	78/99	50/45	26/29
	2.7	3.3	2.8
	1.8-3.9	2.0-5.4	1.5-5.1
Cordless phone,			
>1 year latency	261/701	167/309	81/235
	1.4	1.8	1.2
	1.1-1.8	1.4-2.4	0.8-1.6
>10 year latency	28/45	19/15	8/20
	2.5	5.0	1.4
	1.4-4.4	2.3-11	0.6-3.5
<20, >1 year latency			
Mobile phone	15/14	8/5	2/4
	5.2	7.8	2.2
	2.2-12	2.2-28	0.4-13
Cordless phone			
	14/16	9/6	1/4
	4.4	7.9	1.1
	1.9-10	2.5-25	0.1-10
20-49, >1 year latency			
Mobile phone	208/555	131/221	67/198
	1.5	2.1	1.2
	1.1-2.0	1.5-2.9	0.8-1.8
Cordless phone	138/416	83/179	50/154
	1.3	1.6	1.2
	0.98-1.8	1.1-2.4	0.8-1.8
50-80, >1 year latency			
Mobile phone	123/331	90/148	29/106
	1.3	1.8	0.8
	0.97-1.7	1.3-2.5	0.5-1.3
Cordless phone	109/269	75/124	30/77
	1.5	1.9	1.2
	1.1-2.0	1.3-2.7	0.8-1.9

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

regarding mobile phone use also contralateral use gave a significantly increased risk. We also analysed astrocytoma grade I-II and III-IV separately with no clear difference, although the >10 year latency group had few exposed cases in these calculations (data not shown).

For different age groups highest OR for astrocytoma was found for the subjects that had started the use of a mobile phone at age <20 years, OR=5.2, 95% CI=2.2-12, higher for ipsilateral use OR=7.8, 95% CI=2.2-28, Table I. Similar results were found for use of cordless phone. Thus, first use at age <20 years yielded OR=4.4, 95% CI=1.9-10 increasing to OR=7.9, 95% CI=2.5-25 for ipsilateral use. Lower ORs were calculated for both mobile phones and cordless phones in the two older age groups. No significantly decreased or increased risks were found for contralateral use in the analysed age groups.

For oligodendroglioma and other/mixed glioma no significantly increased risks were found, Table II. In the group of 'other' malignant brain tumours significantly increased risk was found for mobile phone use, >10 year latency, OR=3.2, 95% CI=1.2-8.8 increasing for ipsilateral use to OR=4.1, 95% CI=1.03-16. Analysis of different entities in the group of 'other' malignant brain tumours gave significantly increased OR only for a heterogenic group of

Table II. Odds ratio (OR) and 95% confidence interval (CI) for other malignant brain tumours.[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Oligodendroglioma (n=93)			
Mobile phone,	51/900	28/374	21/308
>1 year latency	1.5	1.7	1.3
	0.9-2.4	0.9-3.0	0.7-2.4
>10 year latency	5/99	3/45	2/29
	1.6	1.6	2.1
	0.5-4.8	0.4-6.1	0.4-11
Cordless phone,			
>1 year latency	38/701	16/309	19/235
	1.4	1.1	1.7
	0.8-2.5	0.5-2.1	0.9-3.2
>10 year latency	3/45	1/15	2/20
	1.8	1.1	2.5
	0.4-7.2	0.1-11	0.5-13
Other/mixed glioma (n=78)			
Mobile phone,	35/900	22/374	13/308
>1 year latency	1.0	1.1	1.0
	0.6-1.7	0.6-2.1	0.5-2.0
>10 year latency	5/99	4/45	1/29
	1.8	2.7	1.1
	0.6-5.3	0.8-9.2	0.1-9.5
Cordless phone,	26/701	17/309	9/235
>1 year latency	1.0	1.1	0.8
	0.5-1.7	0.6-2.3	0.3-1.8
>10 year latency	1/45	0/15	1/20
	0.9	-	1.4
	0.1-7.5		0.1-13
Other malignant (n=71; medulloblastoma - n=6, ependymoma - n=19, other - n=46)			
Mobile phone,	36/900	15/374	5/308
>1 year latency	1.2	1.3	0.4
	0.7-2.1	0.6-2.8	0.1-1.3
>10 year latency	8/99	4/45	1/29
	3.2	4.1	1.7
	1.2-8.8	1.03-16	0.2-15
Cordless phone,	25/701	7/309	7/235
>1 year latency	1.1	0.7	0.9
	0.6-2.0	0.3-1.8	0.3-2.3
>10 year latency	1/45	0/15	1/20
	1.1	-	3.9
	0.1-10		0.3-44

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

4 cases with ipsilateral use. Due to low numbers it was not meaningful to make separate calculations for different age groups of first use of a wireless phone.

Benign brain tumours. Our other pooled analysis reported results for the benign brain tumours from the same study period 1997-2003 (17). The questionnaire was answered by 1,254 (88%) cases and the same control group as for malignant brain tumours was used, n=2,162 (89% respondents).

Acoustic neuroma. Use of mobile phones gave for acoustic neuroma OR=1.7, 95% CI 1.2-2.3, and cordless phones OR=1.5, 95% CI=1.04-2.0, Table III. These ORs increased further for ipsilateral use whereas no significantly increased ORs were found for contralateral use. Using >10 year latency period for mobile phones gave OR=2.9, 95% CI=1.6-5.5 and for cordless phones OR=1.3, 95% CI 0.4-3.8.

Regarding different age groups highest risk was found for first use of a mobile phone at age <20 years, OR=5.0, 95% CI=1.5-16, increasing to OR=6.8, 95% CI=1.4-34 for

Table III. Odds ratio (OR) and 95% confidence interval (CI) for acoustic neuroma (n=243).[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone,	130/900	80/374	48/308
>1 year latency	1.7	1.8	1.4
	1.2-2.3	1.2-2.6	0.9-2.1
>10 year latency	20/99	13/45	6/29
	2.9	3.0	2.4
	1.6-5.5	1.4-6.2	0.9-6.3
Cordless phone,	96/701	67/309	28/235
>1 year latency	1.5	1.7	1.1
	1.04-2.0	1.2-2.5	0.7-1.7
>10 year latency	4/45	3/15	1/20
	1.3	2.3	0.5
	0.4-3.8	0.6-8.8	0.1-4.0
<20, >1 year latency			
Mobile phone	5/14	3/5	1/4
	5.0	6.8	2.4
	1.5-16	1.4-34	0.2-24
Cordless phone	1/16	1/6	0/4
	0.7	1.7	-
	0.1-5.9	0.2-16	
20-49, >1 year latency			
Mobile phone	86/555	59/221	26/198
	2.0	2.5	1.2
	1.3-2.9	1.6-3.9	0.7-2.0
Cordless phone	65/416	48/179	16/154
	1.7	2.2	0.9
	1.1-2.5	1.4-3.6	0.5-1.6
50-80, >1 year latency			
Mobile phone	39/331	18/148	21/106
	1.4	1.1	1.8
	0.9-2.2	0.6-1.9	1.1-3.2
Cordless phone	30/269	18/124	12/77
	1.3	1.3	1.4
	0.8-2.1	0.7-2.2	0.7-2.8

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

ipsilateral use, Table III. Only one case had used cordless phone at age <20 years. In the age group 20-49 years highest OR was calculated for ipsilateral use of both mobile phone and cordless phone, whereas no significant association was found in the age group 50-80 years. Contralateral use yielded no significant associations, but for the age group 50-80 years with OR=1.8, 95% CI=1.1-3.2 for mobile phone.

Meningioma. Regarding meningioma mobile phone use gave OR=1.1, 95% CI=0.9-1.3 increasing to OR=1.3, 95% CI=1.01-1.7 for ipsilateral use, Table IV. For cordless phones OR=1.1, 95% CI=0.9-1.4 and for ipsilateral use OR=1.2, 95% CI=0.9-1.6 were calculated. Using >10 year latency period ORs increased for mobile phones to OR=1.5, 95% CI=0.98-2.4, and for cordless phones to OR=1.8, 95% CI=1.01-3.2. Ipsilateral exposure gave for mobile phones OR=1.6, 95 CI%=0.9-2.9, and for cordless phones OR=3.0, 95% CI=1.3-7.2, in the >10 year latency group.

No clear age-dependent effect was found for meningioma, Table IV. The only significant associations were found for ipsilateral use in the age group 20-49 years, for mobile phone use OR=1.6, 95% CI=1.1-2.2 and for cordless phone use OR=1.4, 95% CI=1.002-2.0.

Other benign brain tumours. Regarding other types of benign brain tumours no significant associations were found overall, Table V. In the >10 year latency group ipsilateral mobile phone use gave OR=4.7, 95% CI=1.1-21. Due to low numbers no separate calculations were made for different age groups. All of these four cases belonged to a heterogenic group of 'other' benign brain tumours.

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for meningioma (n=916).[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone,	347/900	167/374	125/308
>1 year latency	1.1	1.3	1.1
	0.9-1.3	1.01-1.7	0.8-1.4
>10 year latency	38/99	18/45	12/29
	1.5	1.6	1.6
	0.98-2.4	0.9-2.9	0.7-3.3
Cordless phone,	294/701	134/309	101/235
>1 year latency	1.1	1.2	1.1
	0.9-1.4	0.9-1.6	0.8-1.5
>10 year latency	23/45	11/15	7/20
	1.8	3.0	1.1
	1.01-3.2	1.3-7.2	0.5-2.9
<20, >1 year latency	5/14	2/5	1/4
Mobile phone	1.9	2.2	1.7
	0.6-5.6	0.4-13	0.2-16
Cordless phone	2/16	1/6	1/4
	0.5	0.6	1.0
	0.1-2.2	0.1-5.8	0.1-9.5
20-49, >1 year latency	210/555	100/221	74/198
Mobile phone	1.3	1.6	1.2
	0.99-1.6	1.1-2.2	0.8-1.7
Cordless phone	167/416	79/179	54/154
	1.3	1.4	1.0
	0.98-1.6	1.002-2.0	0.7-1.5
50-80, >1 year latency	132/331	65/148	50/106
Mobile phone	1.0	1.1	1.1
	0.8-1.3	0.8-1.5	0.8-1.6
Cordless phone	125/269	54/124	46/77
	1.1	1.0	1.3
	0.8-1.4	0.7-1.4	0.9-2.0

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

Age for use of wireless phones and latency. The median age for cases with astrocytoma was 53 years for use of both mobile phone and cordless phone with no significant difference between persons that reported ipsilateral or contralateral use. Median age was 60 years for no use of a mobile or cordless phone. There was no significant difference for latency between ipsilateral or contralateral use.

Regarding acoustic neuroma median age among mobile phone users was 51 years and for use of cordless phones 47 years. Median age was not significantly different between persons that reported ipsilateral or contralateral use. Cases with no use of wireless phones had median age 57 years. Latency period was not significantly different between ipsilateral and contralateral use.

Laterality according to Inskip. Laterality of tumour was significantly associated with self-reported laterality of use of a mobile phone or cordless phone among cases with astrocytoma or acoustic neuroma, Table VI. Thus, the relative risk (RR) for mobile phone use was 1.7, $p<0.001$ for astrocytoma and for acoustic neuroma RR=1.3, $p=0.01$. Cordless phone yielded for astrocytoma RR=1.5, $p<0.001$ and for acoustic neuroma RR=1.7, $p<0.001$.

Anatomical tumour localisation. Tumours of the astrocytoma type were located in the frontal lobe (n=214), parietal (n=73), temporal (n=169), occipital (n=29), multiple lobes (frontal, parietal, temporal; n=126), cerebellum (n=16) and 'other' (multiple or not defined; n=36). Clearly ipsilateral use of mobile or cordless phones was associated with an increased risk for astrocytoma in the frontal, parietal or temporal lobe (data not in Table). These results were similar, e.g., for the temporal lobe and >10 year latency for ipsilateral mobile phone use OR=3.0, 95% CI=1.4-6.3 and

Table V. Odds ratio (OR) and 95% confidence interval (CI) for other benign brain tumours (n=96 pituaitary adenoma n=34, other n=62).[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
All			
Mobile phone,	49/900	11/374	12/308
>1 year latency	1.5	1.4	2.1
	0.9-2.5	0.5-3.8	0.8-5.3
>10 year latency	7/99	4/45	1/29
	1.8	4.7	2.6
	0.7-4.9	1.1-21	0.2-30
Cordless phone,	34/701	8/309	9/235
>1 year latency	1.5	1.5	2.0
	0.8-2.5	0.5-4.3	0.7-5.5
>10 year latency	1/45	1/15	0/20
	1.3	9.2	-
	0.1-12	0.4-197	

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

Table VI. Analysis of laterality according to the method of Inskip *et al* (19).

Type of phone/laterality of tumour	Laterality of telephone use			Relative risk	P-value[a]
	Left	Right	Total		
Astrocytoma, grade I-IV					
Mobile phone					
-Left	100	58	158	1.7	<0.001
-Right	40	129	169		
-Total	140	187	327		
Cordless phone					
-Left	71	49	120	1.5	<0.001
-Right	32	96	128		
-Total	103	145	248		
Acoustic neuroma					
Mobile phone					
-Left	47	23	70	1.3	0.01
-Right	25	33	58		
-Total	72	56	128		
Cordless phone					
-Left	40	15	55	1.7	<0.001
-Right	13	27	40		
-Total	53	42	95		

[a]Fisher's exact test. Subjects with equal use of both ears were assigned to the same side of telephone use as the side of the tumour.

cordless phone use OR=5.6, 95% CI=1.9-16. No association was found for astrocytoma in the cerebellum or 'other' localisation. Regarding the occipital lobe ipsilateral use of mobile phone with latency >10 years yielded OR=4.8, 95% CI=1.1-21 (n=4 cases) whereas cordless phone did not increase the risk. For astrocytoma in the group of tumour growth in more than one lobe mobile phone use with >10 years latency gave OR=3.0, 95% CI=1.2-7.2 (n=9 cases). No association was found for use of cordless phones in this group.

Table VII. Odds ratio (OR) and 95% confidence interval (CI) for gender-specific analysis of astrocytoma grade I-IV.[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Men (n=405)			
Mobile phone,	255/503	168/215	74/165
>1 year latency	1.6	2.2	1.2
	1.2-2.1	1.5-3.1	0.8-1.7
>10 year latency	69/84	45/38	22/24
	2.5	3.3	2.7
	1.6-3.8	1.9-5.7	1.3-5.4
Cordless phone,	176/318	112/142	57/104
>1 year latency	1.8	2.1	1.5
	1.3-2.4	1.5-3.1	0.9-2.3
>10 year latency	19/31	13/13	6/12
	2.1	4.6	1.4
	1.01-4.4	1.6-13	0.4-4.1
Women (n=258)			
Mobile phone,	91/397	61/159	24/143
>1 year latency	1.2	1.7	0.8
	0.8-1.6	1.1-2.5	0.5-1.3
>10 year latency	9/15	5/7	4/5
	3.4	3.3	4.1
	1.3-8.4	0.9-11	1.01-16
Cordless phone,	85/383	55/167	24/131
>1 year latency	1.1	1.5	0.8
	0.8-1.5	0.97-2.2	0.5-1.4
>10 year latency	9/14	6/2	2/8
	3.6	16	1.4
	1.4-9.3	2.7-90	0.3-7.0

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

The same calculations were made for meningioma. Regarding >10 year latency and ipsilateral use of mobile phone significant association was found for meningioma in the parietal lobe, OR=3.8, 95% CI=1.2-12 (n=5 cases) and temporal lobe, OR=3.1, 95% CI=1.2-8.2 (n=7 cases). In the same group, cordless phone use significantly increased the risk for meningioma in the temporal lobe, OR=10, 95% CI=3.1-34 (n=6 cases). No significant associations were found for the other localisations.

Gender-specific analysis. We made gender-specific analyses for astrocytoma and acoustic neuroma. We found a clear association for both genders. Mobile phone use increased the risk for astrocytoma in men, OR=1.6, 95% CI=1.2-2.1 increasing further to OR=2.5, 95% CI=1.6-3.8 in the >10 year latency group. The results for women were OR=1.2, 95% CI=0.8-1.6 and OR=3.4, 95% CI=1.3-8.4, respectively, Table VII. Also use of cordless phones increased the risk.

Similar calculations for acoustic neuroma yielded a pattern of an association both for men and women, although some of the calculations were based on low numbers, Table VIII.

Attributable fraction. Attributable fraction (AF) is the proportion of cases that can be attributed to the particular exposure. This is calculated as the exposed case fraction multiplied by [(OR-1)/OR]. For astrocytoma grade I-IV use of mobile phone and/or cordless phone yielded AF=16.8% corresponding to 111 cases (95% CI=39-169 cases). AF for acoustic neuroma was calculated to 20.4%, or 50 cases (95% CI=13-77 cases).

Survival. Survival for patients with astrocytoma is age-dependent with better prognosis for younger individuals. We found differences in age for subjects that used wireless phones compared with non-users, see above. Thus, we compared survival only among cases that reported use of a wireless phone. There was no significant difference in survival between ipsilateral and contralateral use of a mobile phone (p=0.95). Median survival of astrocytoma cases with ipsilateral use of a mobile phone was 460 days and for contralateral 543 days. Similarly, no significant differences were found for astrocytoma grade I-II and astrocytoma grade III-IV in separate calculations.

The same analysis for use of cordless phone gave no significant differences in survival for patients with astrocytoma

Table VIII. Odds ratio (OR) and 95% confidence interval (CI) for gender-specific analysis of acoustic neuroma.[a]

Age at first exposure/ Type of telephone	All Ca/Co OR (CI)	Ipsilateral + Ipsi/contralateral Ca/Co OR (CI)	Contralateral Ca/Co OR (CI)
Men (n=105)			
Mobile phone,	76/503	47/215	28/165
>1 year latency	2.3	2.4	2.1
	1.4-3.8	1.3-4.2	1.1-4.0
>10 year latency	15/84	10/38	5/24
	2.9	3.2	3.2
	1.3-6.4	1.3-8.1	0.98-11
Cordless phone,	45/318	32/142	13/104
>1 year latency	2.0	2.1	1.7
	1.1-3.5	1.1-4.0	0.8-3.8
>10 year latency	1/31	1/13	0/12
	0.6	1.2	-
	0.1-5.6	0.1-12	
Women (n=138)			
Mobile phone,	54/397	33/159	20/143
>1 year latency	1.3	1.4	1.0
	0.8-1.9	0.9-2.4	0.6-1.8
>10 year latency	5/15	3/7	1/5
	3.5	3.1	1.6
	1.2-11	0.8-13	0.2-14
Cordless phone,	51/383	35/167	15/131
>1 year latency	1.2	1.4	0.8
	0.8-1.9	0.9-2.4	0.4-1.5
>10 year latency	3/14	2/2	1/8
	2.2	7.5	1.1
	0.6-8.5	0.97-58	0.1-9.2

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

reporting ipsilateral use compared with contralateral use (p=0.87). Median survival for ipsilateral use was 529 days and for contralateral 569 days. No significant differences were found in the groups astrocytoma grade I-II and grade III-IV.

Incidence of brain tumours. We analysed the incidence of brain tumours (ICD-7=193.0) using the Swedish Cancer Registry, available on line (http://www.socialstyrelsen.se/Statistik/statistikdatabas/index.htm). Results are shown for the whole time period 1970-2007 and for different decades, age adjusted to the world standard population, Table IX. During the whole period the annual age adjusted incidence increased significantly for all brain tumours with +0.28%, 95% CI=+0.04 to +0.52. After declining during 1990-1999 an increasing incidence was found during 2000-2007 (+0.56%, 95% CI=-0.99 to +2.13). The age-adjusted incidence of astrocytoma increased during 2000-2007 yearly with +1.55%, 95% CI=-0.15 to +3.27, significantly so among women. In the age group >19 years the annual change was significant for astrocytoma, +2.16%, 95% CI= +0.25 to +4.10.

The annual age-adjusted incidence of acoustic neuroma increased significantly for the time period 1970-2007 with +2.12%, 95% CI=+1.22 to +3.02. However, during 2000-2007 a significantly decreasing incidence was found, -7.10%, 95% CI=-12.4 to -1.42.

Using data published in 'Cancer Incidence in Sweden' (2000-2007), available on line, it is possible to analyse the incidence of nervous system tumours (ICD-7=193) for the time period 2000-2007 in the 6 different medical regions of Sweden reporting to the Cancer Registry, age adjusted according to the Swedish population January 1, 2000. Interestingly, a significantly increasing incidence was found in Gothenburg region (p<0.01) for both men and women whereas all other regions showed for both genders a declining incidence, for example the Stockholm region (p=0.053 for men, p=0.27 for women), Fig. 1. The age adjusted incidence in the Stockholm medical region was in 2007 for men 8.8 per 100,000 person years and for women 11.0. The corresponding rates in Gothenburg medical region were 19.3 for men and 18.8 for women.

Discussion

The main results in our further analyses are consistent with a finding of an increased risk for ipsilateral astrocytoma and acoustic neuroma for use of both mobile and cordless phone.

Table IX. Estimated change in incidence rate/year (%) and 95% confidence interval (CI) for all brain tumours, astrocytoma grade I-IV and acoustic neuroma in Sweden 1970-2007.[a]

	Brain tumour, all		Astrocytoma grade I-IV		Acoustic neuroma	
	Change in incidence rate/year (%)	95% CI	Change in incidence rate/year (%)	95% CI	Change in incidence rate/year (%)	95% CI
Total						
1970-2007	+0.28	0.04, 0.52	+0.05	-0.20, 0.30	+2.12	1.22, 3.02
-1970-1979	-0.15	-1.48, 1.20	-0.16	-1.75, 1.46	-1.66	-9.83, 7.24
-1980-1989	+2.03	0.60, 3.47	+2.53	1.39, 3.69	+4.96	-0.34, 10.5
-1990-1999	-0.32	-1.34, 0.71	-0.33	-1.74, 1.11	+0.72	-2.08, 3.60
-2000-2007	+0.56	-0.99, 2.13	+1.55	-0.15, 3.27	-7.10	-12.4, -1.42
Men						
1970-2007	+0.13	-0.15, 0.41	+0.12	-0.18, 0.42	+2.82	1.78, 3.88
-1970-1979	-0.77	-2.47, 0.96	-1.19	-3.55, 1.23	-1.16	-12.0, 11.0
-1980-1989	+1.41	-0.46, 3.30	+1.72	-0.55, 4.04	+7.29	0.45, 14.6
-1990-1999	-0.93	-1.97, 0.12	-0.21	-1.63, 1.24	-0.29	-2.92, 2.42
-2000-2007	-0.17	-1.94, 1.63	+0.74	-1.67, 3.21	-6.97	-14.5, 1.18
Women						
1970-2007	+0.44	0.20, 0.69	-0.03	-0.35, 0.28	+1.61	0.64, 2.59
-1970-1979	+0.56	-0.86, 2.01	+1.21	-0.78, 3.24	-1.82	-10.4, 7.62
-1980-1989	+2.65	1.26, 4.05	+3.55	2.39, 4.73	+3.31	-2.23, 9.15
-1990-1999	+0.23	-1.21, 1.70	-0.51	-3.02, 2.06	+1.73	-2.63, 6.29
-2000-2007	+1.27	-0.90, 3.48	+2.67	0.69, 4.68	-7.53	-12.7, -2.10
Total, >19 years old						
1970-2007	+0.22	-0.01, 0.46	-0.01	-0.24, 0.22	+2.12	1.24, 3.00
-1970-1979	+0.15	-1.18, 1.51	-0.12	-1.62, 1.41	-1.66	-9.48, 6.83
-1980-1989	+1.54	0.13, 2.96	+2.10	0.75, 3.48	+4.86	-0.37, 10.4
-1990-1999	-0.25	-1.20, 0.71	-0.15	-1.63, 1.34	+0.66	-1.85, 3.23
-2000-2007	+1.26	-0.62, 3.18	+2.16	0.25, 4.10	-7.08	-12.5, -1.30

[a]Calculations based on incidence rates age adjusted to the world standard population.

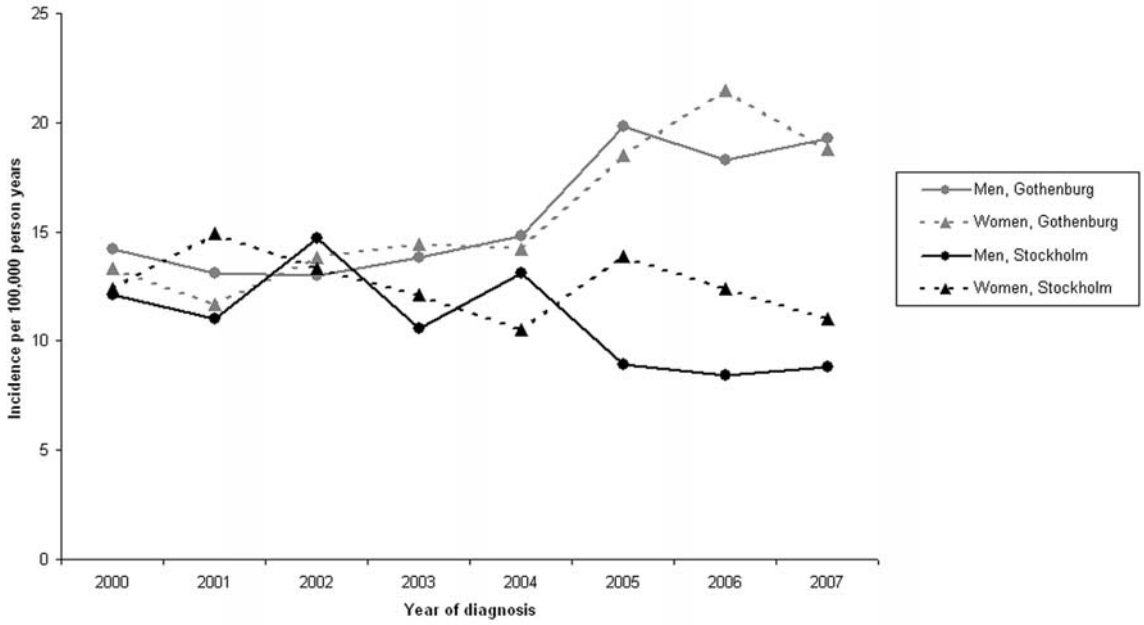

Figure 1. Incidence rates for nervous system tumours (ICD-7=193) in the Gothenburg and Stockholm medical regions, 2000-2007. Age adjusted to the Swedish population January 1, 2000.

Similar results were found when we stratified for gender. For astrocytoma we found an increased risk for tumour in the frontal, parietal or temporal lobe. The risk increased for both tumour types with time since first use and was highest in the group with >10 year latency. This is what one would expect for a carcinogenic effect from radiofrequency fields emitted from wireless phones. The brain is a near-field organ for such exposure, thus all use in a car with external antenna or a handsfree was disregarded. We included in the ipsilateral group all use ≥50% on the tumour side of the head. This is in contrast to our previous analyses where ipsilateral was defined as >50% use and contralateral <50% (16,17). With the now used definition we could include in the calculations the subjects with varying side, that is equally both sides during phone calls, previously analyzed separately.

Especially worrying is the finding of highest risk in persons with first use at age <20 years. This was found both for astrocytoma and acoustic neuroma, except use of cordless phone for the latter tumour, however with only one exposed case. This result is of biological significance since a developing organ is more sensitive for carcinogenic agents and the brain is continuing to develop until ~20 years of age. Cases that had used wireless phones were younger than non-users. To evaluate if such microwave exposure influenced astrocytoma growth we analysed age at diagnosis and latency for ipsilateral and contralateral use, however without finding any significant differences. There was no significant difference in survival for cases with astrocytoma with ipsilateral use compared with contralateral use. Thus, these analyses did not indicate that ipsilateral wireless phone use had a major impact on tumour growth or latency compared with contralateral use, but should be interpreted with caution since also contralateral mobile phone use increased the risk in the >10 year latency group.

It is notable with regard to malignant brain tumour that increased risk was only found for astrocytoma as we have published previously. This type of tumour is a glioma and was included in our review and meta-analysis (6,7). Regarding mechanism for microwave carcinogenesis the astrocytoma finding is of interest, as discussed below.

The results were based on our two consecutive population based case control studies on incident brain tumour cases for the time period 1997-2003. Controls were drawn from the population registry. Exposure was assessed by a questionnaire that was supplemented over the phone, if necessary. In order to get good quality on the information only living cases and controls were included. Thus, deceased patients were excluded, but those with a malignant brain tumour have been included in a further case control study with also deceased controls. These results are to be published separately.

Cases were reported from the regional cancer registries in the study areas. All had histopathological verification of the diagnosis, but if it was unclear copies were obtained from the various pathology departments. Also regarding tumour localisation we received detailed information, mostly based on records from radiology departments. In some instances, e.g. side of an acoustic neuroma, this could be obtained from the report to the cancer registry, but usually radiology records were used.

The case participation was good in our studies, 88% for cases with benign brain tumours, 90% for malignant brain tumour cases and 89% for the controls. One explanation to the high response rate might be that the two studies were hospital-based with many physicians in the research group. Also our study method with questionnaires sent home, usually for cases a couple of months after diagnosis, probably improved the response rate. Thus, cases and controls could answer the questionnaire in a relaxed situation and if necessary give additional information over the phone. Case and control status was obscured during this procedure. Our findings of different risk for different tumour types, increasing risk for latency and ipsilateral use of the wireless phone and no protective effect (decreased OR) for contralateral use strongly argue against both observational and recall bias as an explanation of the findings.

Our method has been judged to be quite superior to the methods in the Interphone studies where computer aided personal interviews were performed, even bedside for the cases (20). Obviously the many different interviewers knew if it was a case or a control that was interviewed. Case participation varied from 37 to 93% and control participation from 42 to 75% in the Interphone studies. Low participation rates for cases and controls might give selection bias and influence the results in the Interphone studies. We have discussed these and other shortcomings in the Interphone studies elsewhere (7,21).

All use of wireless phones using >1-year latency period were included in our studies. Time period for use was assessed including type of phone. Average number of minutes per day was asked for so that total number of hours over the years could be calculated. The unexposed group included subjects with no use or use of wireless phones with ≤1 year latency period. On the contrary, mobile phone use in the Interphone studies was defined as 'regular use' on average once per week during at least 6 months, less than that was regarded as unexposed including also all use within <1 year before diagnosis. This definition of 'regular use' seems to have been arbitrary chosen and might have created both observational and recall bias in the interpretation of such a vague definition.

Use of cordless phones was not assessed in most Interphone studies, in a couple of studies said to have been assessed but with no results clearly presented (22,23). Cordless phones have a median power in the same magnitude as GSM phones (24). They are also used for longer calls than mobile phones (16,17). Including use of cordless phones in the 'unexposed' group, as in the Interphone studies, would thus underestimate the risk and bias OR against unity.

Of interest is our consistent finding of an increased risk for astrocytoma associated with use of both mobile phones and cordless phones. Several animal studies have shown dysfunction of the blood-brain barrier (BBB) caused by radiofrequency fields (25,26). Leakage of albumin into the brain has been demonstrated. The BBB consists of endothelial cells and endfeets of astrocytes. Thus, one mechanism might be that microwaves induce BBB dysfunction so that carcinogenic substances may leak into the brain whereby especially the astrocytes might be exposed. There is some support for that mechanism in our study since we found an increased risk for astrocytoma but not consistently so for other types of malignant brain tumours. Of course also an

interaction with microwaves *per se* might exist since microwaves have been shown to induce several non-thermal effects in experimental studies, including free radicals (27).

Clearly an association between use of mobile or cordless phone and acoustic neuroma was also found. This tumour type is of interest since it is located in an anatomical area with high ipsilateral exposure. One of the first signs of an acoustic neuroma is hearing difficulties. This leads usually to a shift of the ear used during phone calls. Thus it is of importance to assess laterality of phone use for the whole time period and not only most recent use. We were careful about this point for all tumour types. Regarding meningioma there was a tendency to higher OR in the >10 year latency group. However, the results were of borderline significance. It is thus pertinent to wait for results from studies with longer latency periods.

In an editorial in the Swedish Medical Association Journal it was claimed that not much confidence can be attributed to our results of an association between mobile phones and brain tumours since the incidence has not been rising according to the Swedish Cancer Registry (28). However, the completeness of the Swedish Cancer Registry has been seriously questioned (29). Thus, in the year 1998 as many as 13.9% of nervous system tumours were reported to the Hospital Discharge Registry only, but not to the Cancer Registry. From county hospitals 121.1% were never reported and university hospitals missed to report 48.2% to the Cancer Registry. In males aged >70 years 43.9% were never reported and the correspoding frequency for females aged >70 years was 29.6%.

With such large deficits the Swedish Cancer Registry is not reliable to use to determine time trends for brain tumours. Interestingly, in spite of this deficit in the Cancer Registry we found significantly incrasing incidence for brain tumours during the time period 1970-2007. We found for astrocytoma grade I-IV a sharp and significant increase of the incidence during 2000-2007 for subjects >19 years. Considering a tumour induction period of mostly at least 10 years it seems to be justified to analyse that age group and exclude the younger ones. Use of mobile and cordless phones increased rapidly from mid 1990s in Sweden, so these results strengthen our results of an association between wireless phones and brain tumours, since there is no other known risk factor for brain tumours that has been recently introduced in Sweden. It is noteworthy that we found an attributable fraction of 16.8% for astrocytoma.

Taking the still relatively short time for use of wireless phones on a broad scale (30,31) the results showing increasing brain tumour incidence may be early warning of future public health problems, especially considering the large deficit in the Swedish Cancer Registry. It is striking that during 2000-2007 the incidence of nervous system tumours increased significantly in the Gothenburg medical region, which seems to have better reporting than other medical regions in Sweden. The incidence in that region was in 2007 about two times higher than in Stockholm medical region, and there is no other explanation for that than missing data from the Stockholm region. Similar results were also found comparing Gothenburg area with the other four medical regions in Sweden. In spite of this we found significantly increasing incidence for astrocytoma during 2000-2007 in Sweden which is worrying since due to missing data the true increase would even be higher.

The annual age-adjusted incidence of acoustic neuroma increased significantly during 1970-2007, but in contrast to the finding for astrocytoma decreased significantly during 2000-2007. Today the diagnosis is usually based on CT and MRI, so surgery to determine histopathology is thus not always necessary. This is a rare tumour type and centralisation of therapy using e.g. the γ knife (32,33) may partly explain these findings especially since it seems as if some brain tumours from the Stockholm area are apparently omitted from the Cancer Registry. Another possibility is also that patients with this often slowly growing tumour may be on surveillance with MRI without active treatment and might thus not be reported to the Cancer Registry. Thus these results from analysis of incidence data are not consistent with an association between use of wireless phones and acoustic neuroma. We calculated the attributable fraction to be 20.4% in our studies. However, our results are of biological relevance and considering the large deficit in reporting of nervous system tumours to the Swedish Cancer Registry makes a comparison of incidence data with our results less reliable for such a rare tumour type.

In summary, we report a consistent association between use of mobile or cordless phones and astrocytoma grade I-IV and acoustic neuroma. The risk is highest for ipsilateral exposure to microwaves using >10 year latency period. We found an especially high risk for persons that started use of mobile or cordless phones before the age of 20 years, although based on low numbers. The results are supported by increasing incidence of astrocytoma during 2000-2007 in Sweden, significantly so for subjects >19 years old.

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Methodological Aspects of Epidemiological Studies on the Use of Mobile Phones and their Association with Brain Tumors

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Abstract: Our case-control studies were the first to report an association between the use of mobile or cordless phones and brain tumors; glioma and acoustic neuroma. Criticism of these results has been based partly on results from the Interphone studies conducted under the auspice of the International Agency for Research on Cancer (IARC). Here, we compare study design and epidemiological methods used in our studies and the Interphone studies. We conclude that while our results appear sound and reliable, several of the Interphone findings display differential misclassification of exposure due to observational and recall bias, for example, following low participation rates in both cases and controls and bed-side computer guided interviews of cases rather than blinded interviews of cases and controls. However, as we have presented elsewhere, there seems to be a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using $\geq$ 10 years latency period.

Keywords: Acoustic neuroma, cellular phones, cordless phones, case-control studies, methods, Interphone, epidemiology, glioma, microwaves.

INTRODUCTION

An association between use of wireless phones and brain tumors has been increasingly discussed during the last decade. Such devices were introduced on the market in the early 1980's but it was not until the late 1990's that the penetration in the society increased dramatically. A number of case-control studies have been published, and there seems in a meta-analysis of these studies to be a consistent pattern of an association between mobile phone use and ipsilateral glioma and acoustic neuroma using $\geq$ 10 years latency period [1,2]. Thus, for glioma latency period of $\geq$10-years gave odds ratio (OR) = 1.2, 95% confidence interval (CI) = 0.8-1.9 and for ipsilateral use (same side as tumour) OR = 2.0, 95% CI = 1.2-3.4. Contralateral use did not increase the risk significantly, OR = 1.1, 95% CI = 0.6-2.0. Regarding acoustic neuroma OR = 1.3, 95% CI = 0.6-2.8 was calculated using $\geq$10-years latency period increasing to OR = 2.4, 95% CI = 1.1-5.3 for ipsilateral use, but for contralateral use no statistically significant association was found; OR = 1.2, 95% CI = 0.7-2.2. No clear association with meningioma was found [2].

Twelve of the published case-control investigations are a part of the 'Interphone studies'. These were performed in 13 countries and used a common study protocol laid down by the International Agency for Research on Cancer (IARC) and sponsored by industry [3]. According to the contract for these Interphone studies, the funding industry has full access to the publication of results one week before they are publicly available. Some results of these studies have been published in individual countries, see below, but we are still awaiting the final results that seem, now to have been delayed for more than one year [4].

Our Swedish studies were among the first to indicate an association between use of cordless phones and brain tumours [1,2,5-9]. At the moment there are partly conflicting results between our studies and the published Interphone studies, although long-term effects do appear similar. It would seem pertinent therefore to compare the epidemiological methods used in our studies with those used in the Interphone studies in order to better understand the apparent differences in the results. The studies are discussed below, after a discussion of the only cohort study that exists in this area.

MATERIALS AND DISCUSSION

Cohort Study

Two publications resulted from a Danish cohort study [10,11]. The cohort consisted of people that at some time during the thirteen year period between 1982-1995 were registered for the use of mobile phone. According to the first publication following the study in 2001 follow-up continued until 1996 [10]. In that publication results were given for use of analogue (NMT) and digital (GSM) phones, these separate results were not given, however, in the updated publication in 2006 [11].

Results were also given initially for the duration of use of GSM phones. The results recorded 9 persons with brain tumors that had used GSM $\geq$ 3 years and in the same group a somewhat increased standardized incidence ratio (SIR) = 1.2, 95% confidence interval (CI) = 0.6-2.3 was found for brain and nervous system tumors. In the updated publication

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no data were given for duration of use in years. It is to be noted that such data were not reported for NMT phones even in the initial publication [10].

In the latest publication the cohort was followed for seven more years, against the Danish Cancer Registry until 2002. However, the length of time during which mobile phone had been used was not up-dated. The only information that was given was the most general, that is whether or not the cohort member was a user at one point in time; one phone call per week for six months was the initial inclusion criteria. In the calculation of latency, the first year of registration was used, which was usually not equivalent to the total number of years of cellular phone use.

We know that during the first years of the 1980s almost all use of mobile phones was in cars with external antenna. These subjects were thus unexposed to microwaves. No information about that is given. Subjects appear to have been included as exposed although they were not.

More than 200 000 (32%) company subscribers were excluded. In fact, these are the heaviest users and billed 4.5 times higher than laymen in Sweden for example. They started use earlier than others but were included in the "non-user" group of the Danish population; the reference population.

In the study SIR was calculated to 1.21, 95% CI = 0.91-1.58 for temporal glioma, that is the most exposed area of the brain [11]. This finding was based on 54 persons. This should have been divided into phone type and first use i.e. latency period. There was no information regarding the ear used during phone calls and its correlation with tumor site. In our studies we found most consistent increased risk in the category of > 10 years use and the development of ipsilateral tumors [7,8].

Another methodological problem is that expected numbers were based on the general population. However, a large part of the population does use mobile phones and/or cordless phones, and this percent was not assessed at all for the study. This method gives an underestimate of the risk. In the group with first use $\geq$ 10 years significantly decreased SIR of 0.66, 95% CI = 0.44-0.95 was found for brain and nervous system tumors. This is an indication of methodological problems in the study.

Of the subscribers 85% were men and 15% were women, this appears to be a very skewed sex distribution. In fact there seems to be a 'healthy worker' effect in the study since SIR was significantly decreased to 0.93, 95% CI = 0.92-0.95 for all cancers. Certainly early mobile phone users are not socioeconomically representative for the whole of the Danish population as used for comparison in the study.

The authors cite an article [12] that they claim has raised "methodological issues" about our studies on this subject. However, alhough apparently used as an example, the discussion is in the most general terms and may be applied to any or all case-controls studies. In the article Schüz *et al.* [11] failed to cite the following statement in the article "Relying on private cellular network subscription as measure of mobile phone use would also have resulted in substantial misclassification because subscribers bear only a modest relation to users and because corporate users were either excluded or included in the unexposed group" [12,13]. That is in fact the case in the Danish study [10,11].

Furthermore, the cohort only included persons older than 18 years, and in view of our finding that those starting their mobile phone use before the age of 20 are at higher risk than those who started later [14], this represents another problem with the study and its conclusions.

Finally the authors fail to acknowledge the contribution by the telecom industry to the study [11] as cited in the first publication [10], i.e. TelemarkDanmarkMobil and Sonofom. Two of the authors are affiliated with the private International Epidemiology Institute (IEI) of Rockville, MD, USA, which has contributed financially to the study. Where IEI gets its money from is not declared although a connection with the mobile phone industry cannot be ruled out [15,16]. In the application to the Danish national mobile phone programme, that funded part of the study, no mentioning of the involvement or payment of these two consultants was made, a fact that has raised questions.

In summary there are many methodological problems in the study and it is of limited value in its assessment of long-term health effects, as also discussed elsewhere [17,18].

Case-Control Studies

From the Interphone study group eight publications give results for glioma [19-26] and seven for acoustic neuroma [24, 25, 27-31]. There are several methodological concerns that need to be addressed in these Interphone studies. Our own studies in this area are the largest outside the Interphone group and our methods and results must be compared with the Interphone studies, especially as we were the first to find a consistent pattern of an association between use of mobile phones and brain tumours. Furthermore, in contrast to our studies, the use of cordless phones was not assessed in the Interphone studies, or such details were not presented [19,22].

The Swedish Interphone Studies

The Swedish part of the Interphone studies may serve as a model of how these studies were performed using the same core protocol as other Interphone studies. Also, since we are familiar with the Swedish medical system for patients with these tumor types, we have chosen to discuss these two studies in more detail in the following analysis. We discuss in some detail the methods and results of these studies on glioma or meningioma [19], and acoustic neuroma [27]. These studies were part of a medical dissertation [32].

Regarding glioma the Swedish Interphone study [19] reported 23 ORs in Table **2** in the article and 22 of these were < 1.0 and one OR = 1.0. For meningioma all 23 ORs were < 1.0, six even significantly so. These results indicate a systematic bias in the study unless use of mobile phones prevents glioma and meningioma, which is biologically unlikely. It should be noted that several of the overall ORs also in other Interphone studies were < 1.0, some even significantly so. As an example, in the Danish Interphone study on

glioma [20] all 17 ORs for high-grade glioma were < 1.0, four significantly decreased.

In spite of a reported overall decreased risk, an increased risk was found for tumors on the same side of the brain as the cellular phone had been used (ipsilateral exposure) [19]. These calculations yielded for glioma OR = 1.6, 95% CI = 0.8-3.4 for ≥ 10 years time since first regular use. Contralateral use yielded OR = 0.7, 95% CI = 0.3-1.5. The corresponding results for meningioma were OR = 1.3, 95% CI = 0.5-3.9 and OR = 0.5, 95% CI = 0.1-1.7, respectively.

Similarly 23 ORs were presented for acoustic neuroma for various characteristics of mobile phone use in Table **2** from the same study group [27]. Eight ORs were < 1.0, 13 were > 1.0 and two OR = 1.0. No OR was statistically significantly decreased or increased in that table. Time since first regular use of mobile phone ≥ 10 years yielded for ipsilateral use OR = 3.9, 95% CI = 1.6-9.5 and for contralateral use OR = 0.8, 95% CI = 0.2-2.9. Thus, this study confirmed our finding of an association between mobile phone use and acoustic neuroma [33,34].

Both Swedish Interphone studies have some questionable points concerning study participants, statistical methods, and interpretation of the results that are solely the responsibility of the authors [19,27]. In the following paragraphs we discuss some of these issues.

Persons aged 20-69 years living in the medical areas of the university hospitals in Umeå, Stockholm, Gothenburg and Lund in Sweden were eligible. The cases consisted of patients diagnosed with primary glioma, meningioma or acoustic neuroma during September 1, 2000 until August 31, 2002. Unmatched controls were recruited from the population registry. For reasons not disclosed, cases with acoustic neuroma living in the Umeå medical region were not included. This is particularly unfortunate because use of analogue phones has been more common in the northern part of Sweden due to better geographical coverage. Considering our previous findings [33,34] of a significantly increased risk of acoustic neuroma it would have been of special value to include cases from that part of Sweden.

Use of cellular telephones was mostly assessed by personal interviews in the Interphone studies. In contrast to our procedure, the interviewer was aware whether they were a case (patient) or a control, thereby potentially introducing observational bias. It is not described how these personal interviews were organized, a tremendous task considering that vast parts of Sweden from north to south had to be covered. In the sparsely populated and extended area in northern Sweden personal interviews must have meant lots of long distance traveling and imposed additional stress on the interviewers. No information was given in the articles on how or if this methodological problem was solved.

According to the provisions of the Interphone study the interviews were extensive and computer aided. It is likely that such an interview creates a stressful situation for a patient with a recent brain tumor diagnosis and operation. These patients, especially under pressure, often have difficulties remembering past exposures and inevitably have problems with concentration and may have problems with other cognitive shortcomings. According to our experience a better option would have been to start with a mailed questionnaire, that can be answered by the patient during a period of more well-being, if necessary this can be complemented by a telephone interview. This procedure has the additional advantage that it can be accomplished without disclosure during the data collection, whether a person is a case or a control.

The diagnosis of tumor type as well as grading is based on histopathology. X-ray investigation or MR alone is insufficient. Of the 371 cases with glioma in the Swedish Interphone study [19] histopathology examination of the tumor was available for 328 (88%) and for 225 (82%) of meningioma. Thus, it is possible that cases without histology confirmation of the diagnosis may have had another type of brain tumor or even brain metastases. Such misclassifications inevitably bias the result towards unity. It is remarkable that 345 glioma cases were stratified according to grade I-IV, although histopathology was available only for 328 cases. In our studies on brain tumors we have histopathology verification of all of the diagnoses.

For analysis of laterality (ie. the risk of brain tumors on the same side or the opposite side the mobile phone was held during phone calls) an interesting approach was applied in the Swedish Interphone studies. The researchers split the cases into two subsets: those with left and those with right side tumors. Controls were randomly allocated to one of these subsets at a 1:1 ratio. Odds ratios calculated within these subsets were then pooled to give an overall estimate. This method is in principle correct for studies with unmatched controls. However, exposure categorization was questionable for ipsilateral but completely faulty for contralateral use of a mobile phone. Subjects were considered exposed if they used the phone on the same or on both sides of the head. On the other hand, if they used the phone on the contralateral side or did not regularly use a mobile phone they were considered unexposed.

Hence the reference category contained subjects using a mobile phone regularly but reported use on the other side of the head, as the tumor was located. Although exposure to microwaves from mobile phone use is substantially lower on the contralateral side, this discrepancy is less pronounced for regions of the brain (the ventricular and subventricular space) where glioma may originate. Therefore, the chosen procedure introduced exposure misclassification which could have biased the results. For contralateral exposure the opposite exposure classification was used. Patients with tumors on the same side as their exposure were considered part of the reference group. This is an obvious methodological flaw because risk for contralateral exposure would have to be decreased by including ipsilateral exposed cases in the reference group.

It should be pointed out that another weakness in the glioma and meningioma study was that for 33 glioma and 8 meningioma cases information on exposure was obtained from relatives, whereas no relatives of the controls were interviewed [19]. According to our experience relatives have

difficulties in giving information on the use of cellular telephones, especially about the side of the head the phone most frequently used during phone calls.

There are some discrepancies concerning number of cases identified and data in the Swedish Cancer Registry. We used the same criteria for case recruitment from the Swedish Cancer Registry. For example the Cancer Registry contained 469 cases with intracranial glioma cases compared with the 499 in the Interphone study, 337 meningioma cases *versus* 320, and 122 acoustic neuroma cases compared with 160 in the Interphone study [19,27]. The study included cases from neurosurgery, oncology and neurology clinics as well as regional cancer registries in the study areas, and there seems thus to be inconsistency with the numbers in the Cancer Registry.

Among the controls in the glioma and meningioma study 282 (29%) refused to participate [19]. Among some of these non-responders a short interview was made and only 34% reported regular use of a cellular telephone compared with 59% of the responders. If this discrepancy extends to the total group of non-responders the 'true' percentage of mobile phone users in controls would be approximately 52%. Hence this figure would be lower than in glioma (58% exposed) and acoustic neuroma cases (60%). Only for meningioma with 43% exposed cases a lower percentage was reported, however, considering the sex ratio (women:men) for meningioma of about 2:1 a lower percentage of mobile phone users has to be expected due to the lower rate of users among women. It should be noted, however, that a similar procedure in another Interphone study yielded similar results regarding mobile phone use among responders and non-responders [26].

It was discussed in the medical dissertation [32] that: 'Our Swedish study, that includes a large number of long-term mobile phone users, does not support the few previously reported positive findings, and does not indicate any risk increases neither for short-term or long-term exposures.' Considering the methodological shortcomings and that in contrast to the cited assertion of 'a large number of long-term users' the study subjects included only 25 glioma and 12 meningioma cases with long-term use, its conclusion seems to be going a long way beyond what can be scientifically defended.

It should be pointed out that one of the authors (Ahlbom) had stated, before the study started, that an asserted association between cellular telephones and brain tumors is 'biologically bizarre' [35]. This statement might occlude him from objectivity in his own investigation. The REFLEX-study indicates that there are biological mechanisms that could link exposure to the development of diseases such as brain tumors [36].

General Comments

In Table **1** methodological aspects on the Hardell *et al.* and Interphone studies are presented. Several issues may be discussed.

Both sets of studies had the case-control design, included both women and men and were performed during a similar time period, except for the first Hardell *et al.* study that included cases and controls for the time period 1994-1996 [5,6]. Our studies included cases and controls aged 20-80 years, whereas the Interphone studies included various age groups, mostly the age groups 20-69 years or 30-69 years, c.f. [1].

In the Interphone studies deceased cases were included with interviews of relatives, but only living controls. This might have introduced recall bias since it is probably difficult for relatives to know mobile phone habits, ear used during phone calls, type of phone etc. In our studies only living cases and controls were included. It is unlikely that excluding deceased cases would have biased the results unless use of wireless phones gives decreased OR for deceased cases; to balance an increased OR among living cases.

One large difference between our studies and the Interphone studies was assessment of exposure, as discussed above. We used postal questionnaires that were blinded as to case or control status during assessment of exposure and data coding. The questionnaire was sent home to the cases, in general about two months after the diagnosis. This gave a more relaxed situation for the cases compared with the Interphone studies where mostly bedside interviews were performed during the patients' stay at the hospital, some even newly operated upon.

Obviously in the Interphone studies the case and control status was known during the interviews and processing of data in the computer. Observational bias might have been introduced in these studies since the interviewer knew if it was a case or control that was being interviewed. In contrast, assessment of exposure and all further data processing until statistical analysis was blinded as to being a case or a control in our studies. Assessment of exposure was similar for cases and controls.

It might have been a stressful situation for the cases with bedside interviews in the Interphone studies creating recall bias. In one of the Interphone studies Mini-Mental State Examination was completed by 80% of the cases and 90% of the controls [20]. It was concluded that patients scored significantly lower than controls due to recalling words (aphasia), problems with writing and drawing due to paralysis. Certainly these cognitive defects would not be expected to the same extent for patients with acoustic neuroma and clearly in the Swedish Interphone studies the results for acoustic neuroma [27] seem to be more sound and reliable than for glioma and meningioma [19].

We included use of mobile or cordless phone 'any time' in the exposed group and made dose-response calculations based on number of hours of cumulative use. The unexposed group included also subjects with use of wireless phones with $\leq$1 year latency period.

On the contrary, mobile phone use in the Interphone studies was defined as 'regular use' on average once per week during at least 6 months, less than that was regarded as unexposed including also all use within < 1 year before diagnosis. This definition of 'regular use' seems to have been arbitrarily chosen and might have created both observational

Table 1. Methodological Aspects on the Hardell *et al.* and Interphone Studies.

Study Design, Methods	Hardell *et al.*	Interphone
Type of study	Case/control	Case/control
Study period	1994-1996 [5,6] 1997-2003 [7,8]	Varying 1999-2004
Cases	Cancer registry	Hospitals (some checks with cancer registry)
Controls	Population registry	Populating registry/Practitioners list/ Random digit dialling
Status	Only living cases/controls	Also deceased cases included with proxy interviews Only living controls
Assessment of exposure	Questionnaire	Computer guided personal interview
Type and time for interview	*Cases:* about 2 months after diagnosis. Mailed questionnaire. *Controls:* Mailed questionnaire	*Cases:* Bedside (mostly) face-to-face by nurses or medical students *Controls:* Face-to-face interviews usually in their home
Interview	Blinded as case or control	Not blinded as to case or control
Mobile phone use	Assessed	Assessed
Cordless phone use	Assessed	Not assessed (except for two studies)
Exposure, latency	Start $\leq$ 1 year before diagnosis disregarded for cases. Same year for the matched control	< 1 year before diagnosis disregarded for cases. Referent date for controls = date of identification or mean of diagnosis date for cases
Exposure, time	Yes = any use; starting > 1 year before diagnosis	Yes = Regular mobile phone use on average once per week during at least 6 months; starting $\geq$ 1 year before diagnosis (see above).
Unexposed	No use of mobile or cordless phones or use starting $\leq$ 1 year before diagnosis	No or not regular mobile phone use or use < 1 year before diagnosis (see above). Note: use of cordless phone included in the unexposed group
Blinded coding	Yes	No. Computer based interviews with knowledge if it was a case or control
Data processing	Blinded as to case or control	Not stated (not blinded?)
Data used in presentation	Anytime (DECT or mobile phone)	Regular user

and recall bias in the interpretation of such a vague definition.

Use of cordless phones was not assessed or not clearly presented in the Interphone studies, e.g. [19, 22]. We found a consistent pattern of an association between cordless phones and glioma and acoustic neuroma [7,8]. It has been shown that the GSM phones have a median power in the same order of magnitude as cordless phones [37]. Moreover, cordless phones are usually used for longer calls than mobile phones [7,8]. Including subjects using cordless phones in the "unexposed" group in studies on this issue, as for example in the Interphone investigations, would thus underestimate the risk and bias OR against unity.

In Table **2** we present response rates for cases and controls in the various studies. The case participation was good in our studies, 88% for cases with benign brain tumours, 90% for malignant brain tumour cases and 89% for the controls. On the contrary case participation varied from 37% to 93% and control participation from 42% to 75% in the Interphone studies. Obviously low participation rates for cases and controls might give selection bias and influence the results in the Interphone studies.

Methodological issues in the Interphone studies have been discussed elsewhere [38,39]. It was concluded that the actual use of mobile phones was underestimated in light users and overestimated in heavy users. Random recall bias could lead to large underestimation in the risk of brain tumours associated with mobile phone use. It was further suggested that selection bias in the Interphone study resulted in under selection of unexposed controls with decreasing risk at low to moderate exposure levels.

The Interphone studies have been discussed in letters to the Editor regarding e.g. the German study on glioma and meningioma [22,40], the UK study on glioma [21,41,42], the study on acoustic neuroma in five countries [29,43-45], the Swedish study on glioma and meningioma [19,46], and the Danish study on acoustic neuroma [28,47,48]. Thereby similar critique as in this presentation has been made.

Table 2. Response Rates (Percent) in the Hardell *et al.* and the Interphone studies. Numbers of Interviewed Cases is Given. Note that for the Hardell *et al.* Pooled Results are Given from Previously Published Original Results

Study	Response (Number and Percent)	
	Cases	Controls
Hardell *et al.* (Sweden) 2006 [7,8]		
- Benign brain tumors	1 254 (88%)	2 162 (89%)
- Malignant brain tumors	905 (90%)	
Lönn *et al.* (Sweden) 2004 [27]		
- Acoustic neuroma	148 (93%)	604 (72%)
Lönn *et al.* (Sweden) 2005 [19]		
- Glioma	371 (74%)	674 (71%)
- Meningioma	273 (85%)	
Christensen *et al.* (Denmark) 2004 [28]		
- Acoustic neuroma	106 (82%)	212 (64%)
Christensen *et al.* (Denmark) 2005 [20]		
- Glioma	252 (71%)	822 (64%)
- Meningioma	175 (74%)	
Schoemaker *et al.* (Five North European countries) 2005 [29]		
- Acoustic neuroma	678 (82%)	3 553 (42%)
Hepworth *et al.* (England) 2006 [21]		
- Glioma	966 (51%)	1 716 (45%)
Schüz *et al.* (Germany) 2006 [22]		
- Glioma	366 (80%)	1 494 (61%)
- Meningioma	381 (88%)	
Takebayashi *et al.* (Japan) 2006 [30]		
- Acoustic neuroma	101 (84%)	339 (52%)
Klaeboe *et al.* (Norway) 2007 [25]		
- Glioma	289 (77%)	358 (69%)
- Meningioma	207 (71%)	
- Acoustic neuroma	45 (68%)	
Lahkola *et al.* (Five North European countries) 2007 [23]		
- Glioma	1 521 (60%; range 37-81%)	3 301 (50%; range 42-69%)
Hours *et al.* (France) 2007 [24]		
- Glioma	96 (60%)	455 (75%)
- Meningioma	145 (78%)	
- Acoustic neuroma	109 (81%)	
Schlehofer *et al.* (Germany) 2007 [31]		
- Acoustic neuroma	97 (89%)	194 (53 %)
Takebayashi *et al.* (Japan) 2008 [26]		
- Glioma	88 (59%)	196 (53%)
- Meningioma	132 (78%)	279 (52%)
- Pituitary adenoma	102 (76%)	208 (49%)

CONCLUSION

Our study group was the first to report a consistent pattern of an association between wireless phones and glioma and acoustic neuroma, whereas this was not found for meningioma. Meta-analysis of all published studies in this area using a reasonable latency period of at least 10 years confirmed this finding for use of mobile phones and ipsilateral

glioma and acoustic neuroma, but no significant association was found for meningioma [1,2]. Our studies have been attacked by unfounded critique as we have explored in detail elsewhere [37], but also in the publications presenting our case-control studies. Based on a comparison between our studies and the Interphone studies our results seem to be sound and reliable whereas several of the Interphone findings are prone to differential misclassification of exposure due to e.g. observational and recall bias.

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Mobile telephones and cancer: Is there really no evidence of an association? (Review)

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Abstract. Two Swedish epidemiological studies have shown an association between the use of mobile telephones, mainly of the analogue type, and brain tumours. These findings have been corroborated in a Finnish study. Supportive evidence has also come from studies in USA, but these investigations, as well as a Danish study, are inconclusive due to e.g., few exposed subjects, short latency periods and methodological shortcomings. The Swedish Radiation Protection Authority (SSI) engaged two epidemiologists from a private company to conduct a review of the literature. They claimed that use of mobile telephones is not associated with increased risk for brain tumours. Their conclusion was, however, based on an unbalanced view of current literature in favour of studies showing no association. These circumstances are further explored in this communication.

Contents

1. Introduction

The Swedish Radiation Protection Authority (SSI) recently engaged two US epidemiologists to review published epidemiological studies on the relationship between the use of mobile telephones and cancer risk. They were Drs John D. Boice Jr and Joseph K. McLaughlin from the private company International Epidemiology Institute (IEI). In their review [(1), here referred to as the SSI report], they claimed that no consistent evidence was observed for increased risk of brain cancer, meningioma, acoustic neuroma, ocular melanoma, or salivary gland cancer due to mobile phone use.

However, these two epidemiologists were co-authors of the Danish cohort study by Johansen *et al* (2), which is among the reviewed studies. The Danish Cancer Fund, two Danish mobile phone net operators and IEI financed this study. Boice and McLaughlin were also co-authors of the Danish melanoma study by Johansen *et al* (3). Additionally, one of the US studies (4) that was classified as well designed in the SSI report was preceded by a publication on study design (5). In this publication John Boice was co-author. Inskip *et al* (4) referred regarding material and methods to that particular article about study design: 'the study methods have been described in detail previously' (5). Thus, the very positive words by Boice and McLaughlin about these studies should be viewed with this as background. John Boice and Joseph McLaughlin did not declare if they had any conflict of interest.

The letter from the SSI to Dr Boice asking for 'evaluation of epidemiological studies on cellular telephones and cancer risks' was dated 15th May, 2002. The letter stated that 'the report should be ready within 2 to 4 weeks after the publication of the new Swedish data'. In fact the Swedish studies constituted two of the reviewed 10 epidemiological studies, but of the 14 pages discussing all studies, 7 pages were devoted to the two Swedish studies alone.

The aim of the SSI report was to give a balanced presentation of the evidence, which in our opinion was not achieved. A balanced presentation should view the evidence from all sides. Starting from the hypothesis of no association, what are the strengths of the studies showing no effect and what are the weaknesses of those showing an effect. But the review should also look the other way: if actually there is an association, what are the strengths of the studies showing an effect and what are the weaknesses of those that do not? In the present case the discussion is highly unbalanced in favour of those studies that did not show biological effects of exposure to emissions from mobile phones.

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Key words: brain tumours, cellular telephones, cordless phones, Swedish Radiation Protection Authority (SSI)

The Swedish studies by Hardell *et al* (6-8), which demonstrated an association between the use of cellular phones and cancer, and a few studies that addressed this concern in the United States are considered 'non-informative' by Boice and McLaughlin, either because the follow-up was too short or numbers of cancers too small (USA) or because of 'methodological limitations' (Sweden).

According to the authors, there are five well-designed epidemiological studies, conducted in three countries and using different designs: three hospital-based case-control studies in the United States (4,9,10), a registry-based case-control study in Finland (11), and a registry-based cohort study of over 400,000 cellular phone users in Denmark (2). Boice and McLaughlin find a consistent picture from these studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date.

Furthermore, they say that the emerging results of experimental studies have failed to confirm earlier reports of possible adverse outcomes from radiofrequency exposure, and that there is no biologically plausible mechanism known today supporting a carcinogenic effect of non-ionising radio-frequency fields.

This report caused the SSI to send out a press release about the possible risks associated with the use of cellular phones stating: 'the current state of the science is reassuring'. But is the knowledge such that we can say it is reassuring? We shall here look closer at the so-called well-designed studies and give our views on why we do not consider them to support this view.

2. Epidemiological studies

Johansen *et al* (2) performed a population based cohort study comprising all mobile phone users in Denmark from 1982 up to 1995, a total of over 700,000. Those with a company paid phone were discarded, about 200,000. The duration of use was given only for digital (GSM) subscribers, of whom 93% had less than 3 years of mobile phone use. A non-significant risk increase was seen for GSM-users with ≥3 years duration of use, standardised incidence ratio (SIR) = 1.2 (95% CI = 0.6-2.3), and digital phone users that previously used an analogue phone (SIR) = 1.3 (95% CI = 0.8-2.1). For analogue phones these analyses were not reported. The risk for occipital lobe glioma was insignificantly elevated (SIR 1.8), but not temporal and parietal tumours. The argument by the SSI review authors that occipital lobe is less irradiated is not correct for all types of cellular telephones, especially not for older analogue types that account for the highest proportion of person-years accumulated in this study. Any exposure assessment other than being a subscriber was not done, which may lead to misclassifications since many private users are sharing their phone with other members of the family.

Considering the methods of the study, one has to ask whether this study could have found an elevated brain cancer risk if there was one. The most important prerequisite for the study of non-ionising radiation induced brain tumours is to allow for reasonable latencies. Although there is broad agreement that microwaves cannot directly induce malignancy, a contribution of exposure during the initiation phase or during tumour growth cannot be ruled out. These hypotheses have to be considered separately. Concerning contribution during the initiation phase, there is convincing evidence for average latencies of more than 5 years for brain tumours. In the cohort there were only about 8% that could be used for such an analysis. The expected annual number of brain and nervous system tumours in this sub-cohort is about 1-2 cases. The analysis for latency in the article by Johansen *et al* (2), given in their Table III, has apparently accumulated these cases over the total period of phone use without allowing for a reasonable latency period (e.g. disregarding all cases earlier than 5 years after first use of a mobile phone).

Overall the power of the study of Johansen *et al* (2) to detect a 50% increase of brain tumour incidence in long-term mobile phone users under the given latency constraints is negligibly small. If on the other side we consider the hypothesis of a contribution of mobile phone use on brain tumour growth we have to differentiate the types of brain tumours. There are gross differences in growth rates between different types of tumours, ranging from weeks between first clinical signs and diagnosis to decades. It is difficult to detect an influence of mobile phone use on growth rate of fast-growing tumours, like glioblastoma, in such a cohort study. Hence, considering influence on growth rate, all glioma brain tumours of grades III and IV should be analysed separately. If mobile phone use increases growth rate of slowly growing brain tumours, what is the consequence with respect to cumulative incidence? Depending on the ratio of observation to manifestation duration an increase of incidence can be expected. However, the observation period (in this study an average of 3.1 years after first use of a mobile phone) was too short to detect such an effect, as also the authors conceded: 'latency may be too brief to detect an early-stage effect or an effect on the more slowly growing brain tumours'. Hence the study cannot contribute to the assessment of a possible role of mobile phone use on brain tumours. This evaluation also holds, mutatis mutandur, for malignant diseases of the haematopoietic and lymphatic tissue.

The authors refer to an American study (12) that showed that 48% were not the only users of the phone. They also write about the limitations in their study: 'our study may currently have too few heavy users to exclude with confidence a carcinogenic effect on brain tissue following intense, prolonged use of cellular phones'. Although this reservation is quite weakly expressed, considering that they had no data on intensity of use, and in over 40% not even data on duration of use, even this statement seems to have been forgotten by Boice and McLaughlin as as well the SSI when drawing their conclusions about the current knowledge.

Muscat *et al* (9) studied malignant brain tumours in patients from five different hospitals in the US. Data from 469 cases and 422 controls matched for sex, age, race, hospital and month of admission were available. Controls were hospital patients, but except for two hospitals not cancer patients. In contrast to the Swedish studies (6-8) interviewers of patients were not blinded to case status, and time of interview differed substantially between cases and controls. Both points might have biased results towards the null hypothesis, especially the second one. It is definitely wrong that recall bias usually results in spurious positive findings, as the authors argued. The effect of recall bias on the odds ratio depends on the height

and sign of the correlation between bias and case status. In the present study by Muscat *et al* (9) most case patients were interviewed within two days after surgery. Thus, if there were recall bias it would have been positively correlated with brain tumour diagnosis and hence would have reduced a possible association!

Out of the 469 cases included in the study only 66 had been using mobile phones, and the corresponding number among the controls was 76 out of 422. The exposure in mobile phone users was such that 86% of the cases and 85% of the controls had been using an extended antenna during the calls. Of all the phones, 88% were analogue and 50% of one brand. The duration of use was on average 2.8 years for the cases and 2.7 years for the controls. The mean usage time per month was 2.5 and 2.2 h for cases and controls, respectively. The study population is thus very small and with extended antenna the exposure to microwaves in the brain becomes low and area of exposure is shifted to parietal and occipital locations. Together with the short time of usage this study is not very informative.

However, it should be mentioned that of the 41 cases in the study with information about laterality, 26 had been using the phone on the ipsilateral and 15 on the contralateral side. Overall the odds ratio (OR) associated with use of a handheld cellular telephone was 0.8. The highest histology-specific risk estimate was found for neuroepitheliomatous cancers with an OR of 2.1. However, it seems that diagnosis was not unequivocal in all cases. Comparison with the distribution of histological types between users of handheld cellular telephones and non-users reveals a highly significant difference ($p<0.001$), due to an increased frequency of neuroepitheliomatous cancers (21% vs. 5%) and a reduced frequency of glioblastoma (44% vs. 53%) and astrocytoma (11% vs. 19%). One of the most severe methodological problems of the study is the predominance of glioblastoma, comprising more than half of the cases. Glioblastoma are of highest malignancy (grade IV) and have a very high growth rate with weeks to at most months from first disease signs to diagnosis.

If emissions from mobile phones were considered as a factor influencing any stage of the malignant process, tumour locations at the irradiated area have to be chosen; otherwise the chance to detect an association would be substantially reduced.

Concerning the significant difference in morphological types of brain tumours between users and non-users of mobile telephones there are at least two explanations. First, exposure to emissions from mobile telephones increases growth rate of already initiated brain tumours; this would have an noticeable effect only on slowly growing tumours, because e.g. a latency decrease of glioblastoma from 2 months to 1 month would have no effect on annual incidence, while in low-grade astrocytoma a decrease from 2 years to 1 year would increase incidence. Another explanation would be that patients that develop high-grade brain tumours avoid using mobile telephones. However, this explanation is unsatisfactory because these patients often have no early clinical signs while those developing low-grade tumours may experience years of various symptoms that are more likely to result in avoidance of mobile telephones. It is also possible that the effect is due to confounding by age, because older patients might have less history of cellular telephone use and at the same time more often experience high-grade tumours. However, the effect on histological type seems to be too strong to be solely due to age. In fact, it can be shown that even considering age as a confounder, the data are compatible with an increased growth rate in mobile phone users.

Muscat, the principle author of this study (9), participated in a meeting in Paris, where he reported on the study but giving an OR of 2.2 [95% confidence interval (CI) = 1.0-4.7] for neuroepithelioma (13). There is still another publication from this study (14), and now the OR is 2.6 (95% CI = 1.2-5.4). We have no explanation for this discrepancy. The publication gives no account of the procedure to assess histological types. Neuroepithelioma can unambiguously be diagnosed only by immunohistological methods. In the absence of data on immunostaining there is always a possibility to shift cases between ganglioglioma and mixed types. We do not know, however, whether or not such allocation problems occurred.

In summary, the study of Muscat *et al* (9) has a number of methodological deficiencies, most important the short latency, the predominance of glioblastoma, and the too small number of tumours that can possibly be considered in a study of localised exposure. Note that already in 1948 several conditions for irradiation induced tumours have been established, among these: exposure must precede diagnosis by at least 5 years and localisation of tumour must be at the irradiated site (15). It is worth mentioning that in the Paris report (13) Muscat writes: 'although the current study shows no effect with short-term exposure to analogue cell phones, further studies are needed to account for longer induction periods and for the possible effects of GSM phones'.

The exposure to mobile phones is also of short duration in the study by Inskip *et al* (4). They also did a hospital based case control study comprising 782 cases collected during 1994-1998. They enrolled 489 patients with primary malignant brain tumours (glioma or neuroeptheliomatous tumours) but also 197 patients with intracranial meningioma, and 96 patients with acoustic neuroma. Overall 799 hospital based control patients were frequency matched by sex, age, ethnic group, and proximity of residence to hospital. No increased risk was observed either for primary malignancies or for meningioma or acoustic neuroma. Also no association was found with the side of the head the telephone was typically used when phoning. Difference in distribution of histological types between users and non-users was highly significant ($p<0.0001$) as in the study by Muscat *et al* (9). This difference was due to a pronounced reduction of the frequency of glioblastoma (57% in non-users vs. 27% in users) and an increase in astrocytoma (12% vs. 21%), oligodendroglioma (15% vs. 27%) and other glioma (6% vs. 11%). Also neuroepithelomatous tumours were more frequent in users, however, the difference was less pronounced as in the study of Muscat *et al* (9), possibly reflecting differences in diagnostic procedures. The difference, however, that is consistent between both studies, is that between high-grade and low-grade tumours, fast and slowly growing ones. In both studies the frequency of low grade, slowly growing tumours was substantially higher in mobile phone users as compared to non-users. Also in the study of Inskip *et al* (4) the authors did not note this important effect. Because of this important and yet unexplained difference, further investigation should put emphasis on the determination of growth rate.

However, only 2.6% of the cases and 3.3% of the controls had used phones regularly for more than 5 years (4). The authors did not state anything about use with extended antenna but since the study was done at about the same time as Muscat *et al* did their study (9) it can be assumed that the same is valid here and thus the majority may have been using the phone with extended antenna. Thus, also here the study population is small and the exposure is low, something that the authors also point out: 'potential risks associated with digital phones or higher operating frequencies could not be addressed'. Furthermore they say: 'they are not sufficient to evaluate the risks among long-term, heavy users and for potentially long induction periods'. A small increased risk for anaplastic astrocytoma was seen with OR = 1.8 (95% CI = 0.7-5.1), but Boice and McLaughlin chose to disregard this in their review. Also for acoustic neuroma a risk increase with OR = 1.9 (95% CI = 0.6-5.9) was found among those who had used a mobile phone ≥5 years.

A second report by Muscat *et al* (10) about mobile phones and acoustic neuroma contains strong evidence for a reversal of cause and effect: they found a higher incidence of acoustic neuroma at the contralateral side (with respect to predominant mobile phone use), which is consistent with the assumption that cases tended to change the side of phone use because of hearing problems caused by the growth of the tumour. This is totally according to expectation but points to the insufficient latency because it indicates that mobile phone use followed and not preceded the development of the disease. The side of the phone could also have been misclassified if information on the used ear was not assessed for the whole period of use.

Auvinen *et al* (11) studied brain tumours among 398 cases diagnosed during 1996. Also in this study the total number of users was low, only 13% of the cases had ever had a mobile phone subscription. The inclusion time was very short, for analogue (NMT) users 2-3 years and for digital (GSM) less than one year. They reported an increased risk for glioma, OR = 2.1 (95% CI = 1.3-3.4) for NMT users whereas for GSM the OR was 1.0. When the duration of use of analogue phones was analysed as a continuous variable a significant risk increase with 20% per year was seen for glioma, OR = 1.2 (95% CI = 1.1-1.5). Boice and McLaughlin did not discuss this finding. Auvinen *et al* (11) concluded that further studies with a larger number of cases and a better exposure assessment and longer exposure duration are necessary for a meaningful risk assessment.

The five studies (2,4,9-11) mentioned in the SSI report (1) as corroborating the hypothesis of no association, have in common that they covered very few cancer cases with mobile phone use and they also had very short duration of use. None of the studies can in principle say anything about GSM use since the study time often had ended in the mid 1990's when GSM systems were only shortly in operation.

Regarding the studies by Hardell *et al* (6-8) the argumentation for a dismissal becomes erroneous with direct misquotes (1). On page 9 in their summary it is said that the risk for tumours among analogue phone users is 1.3 but for latency times >5 years the OR is 1.1. According to Table II in Hardell *et al* (8) the OR for >5 years was 1.4 (95% CI = 1.04-1.8). There is a further increase for latency time >10 years to OR = 1.8 (95% CI = 1.1-2.9). Boice and McLaughlin avoid mentioning that the highest risk was shown in the group with the longest exposure time.

3. Methodological aspects

In their critique of the Hardell *et al* study (8) the SSI report claims that the cordless phones have 25-100 times lower power output than GSM phones. This statement does not take into account that the GSM phone regulates the output power depending on the quality of transmission, and measurements show that for instance in Stockholm city the GSM 900 phones only use 4% of the maximum output power as a median value (16). A test phone to be used in the Interphone study gives even lower value of 2%. Furthermore, the DTX function which makes the phone transmit with 217 pulses per second when one is talking, but only with 2 pulses per second when listening, in principle causes a further reduction with a factor of up to two. If one also takes into account a SSI report on measurements on phones showing that most phones have less than 1 W output power instead of the allowed 2 W in the standard, this leads to that the GSM phones have a median power of 10-20 mW, thus, the same order of magnitude as the cordless phones. With the longer calling time with cordless telephones the 'dose' for cordless users is then even higher than for that of the GSM users!

Let us also review some of the statements indicating lack of epidemiological accuracy. Some results in the Boice and McLaughlin report are given without stating the number of individuals involved. Some of the confidence intervals will become wide because of the low number of long-term users. The discussion about risk with regard to laterality is strange. They avoid mentioning that the significant results were found for ipsilateral phone use, while no increased risk was seen for contralateral use. They also carry out an unscientific discussion about dose-response depending on the type of phone used by the person. The only thing that can be said in this respect is about total number of hours of use for the different phones, but also here the knowledge is imprecise because no data about SAR were possible to obtain.

Boice and McLaughlin make a rather remarkable statement about the inclusion criteria in the Hardell *et al* (6-8) studies that only included patients alive at the time of the investigation 'study results based only on survivors are likely to be distorted since the surviving cases represent a highly selected group'. Since a significantly increased risk was found in the overall material for analogue phones, OR = 1.3 (95% CI = 1.02-1.6) and a particularly high risk for acoustic neuroma, OR = 3.5 (95% CI = 1.8-6.8) their statement means that mobile phone use should have a preventive effect for development of brain tumour among persons dying shortly after their operation, thus particularly for the malignant tumours. To get a total risk of 1.0 a decreased risk is needed among the deceased. That is not biologically plausible. Furthermore, it is not clear how their statement can be valid for acoustic neuroma, which has a good prognosis.

Let us close this by some remarks about study design. Both the Hardell *et al* (6-8) and the three US studies (4,9,10) were case-control studies and standard methodology was used. In general the Swedish studies can be considered to be the

better ones from a methodological point of view by their access to different registers. The US studies were using hospital patients as controls, which is a selected group and cannot be considered representing the general population. All studies used questionnaires to assess exposure. In the Muscat *et al* study (9) the interviews were done with the patients at bedside within a few days after a brain tumour surgery. Also in the Inskip *et al* study interviews were done at hospitals (4). It can be discussed how valid the answers may be with regard to the situation with a recent operation with anaesthesia, ongoing drug therapy and the trauma the diagnose itself means. In the Swedish studies the interviews were done in a quiet stage a few months after surgery and in the home of the patients. This is an advantage compared to the other procedures.

Boice and McLaughlin bring forward no factual reasons for the statements about the Swedish studies being non-informative. They complain about the detailed presentation of the results and state that this may mean that the results are found by 'chance' without discussing the biological plausibility of the results. Detail reporting is more scientifically valid than just selecting some of the results. Let us quote the study by Auvinen *et al* (11): 'in conclusion, information obtained directly from subjects on mobile phone use seems preferable to a register-based approach, which has insufficient level of information'. This should have been something for Boice and McLaughlin to consider in their review of the studies they themselves participated in.

4. Experimental studies

Concerning experimental studies it is concluded in the SSI report that the only positive report on an association between exposure to mobile phone type signals and cancer (17), now can be refuted since another study with the same type of transgenic mice did not find any effect (18). However, these two studies are very different in design and it is not possible to draw that conclusion. Repacholi *et al* (17) exposed the mice 30 min before light on at 06:00 and another 30 min 12 h later before light off for 18 months. Utteridge *et al* (18) exposed the animals for 60 min during daytime, 5 days per week, for 24 months. What influence has these different timings of exposure, both the intermittence and the time of the day? Can it be said that 2x30 min is equal to 1x60 min? Today we do not have an answer to this. In radiation therapy fractionated doses are used, i.e. two treatments per day, to reduce the repair time of the cell damage.

Another difference between the two studies is that in the first one the animals were free to move in their cages during exposure while in the second one they were restrained in tubes. The latter is better from a dosimetrical point of view but instead a stress reaction cannot be ruled out. To what extent this would influence the cancer development is not precisely known. It should, however, be noted that immobilisation stress might obscure an effect of exposure (19).

The allusion to the study of Utteridge *et al* (18) should suffice as an example how the evidence has been distorted: 'thus it can be concluded that the Repacholi *et al* (17) study has been refuted, which is of importance because this was the only experimental evidence suggesting a carcinogenic effect from RF exposure in the animal literature'. Even a beginner in science knows that only the hypothesis of no effect can be refuted, while a positive finding cannot be balanced by a negative result. The chance to erroneously accept the hypothesis of no effect is in most cases considerably higher as the chance to erroneously reject the hypothesis of no effect! But there are many other reasons, material ones, why the result by Utteridge *et al* (18) is doubtful; however, the SSI report takes it for granted.

5. Interaction mechanisms

The mechanistic understanding of how low intensity microwaves affect living tissue is unfortunately almost non-existent. Interestingly enough, findings from several experimental systems, i.e. cells, worms and chick embryos (20-22) show that the exposure affects the expression of stress proteins (heat shock proteins, hsp). It is still not established if these changes only are of positive character or if they can lead to detrimental effects.

French *et al* (23) have in a review article proposed the hypotheses that radiofrequency fields can cause chronically increased levels of a specific protein, hsp70. A short increase is a normal and powerful defence mechanism, but according to French *et al* (23) long-term increased levels may cause an increased risk of tumour formation. The area is, however, to a large extent unexplored.

6. Concluding remarks

With this as a background we find it remarkable that the authors of the SSI report can put forward the cohort studies and the hospital-based case control studies in the way they are doing without considering the shortcomings in these studies, and the limited possibility they offer for making a statement about long-term heavy use of cellular phones, especially of the digital type. They conclude: 'in our view, a consistent picture has emerged from these studies that appears to rule out, with a reasonable degree of certainty, a causal association between cellular telephones and cancer to date'. In the hands of other authors of reviews that would take into account all the existing data as well as the shortcomings that appear in the studies, both the epidemiological ones and the experimental work, the conclusion may very well have been the complete opposite: 'in our view, a consistent picture is emerging from these studies that a causal association between use of cellular phones and brain tumours cannot be ruled out'.

The current state of knowledge is thus not reassuring and further research is needed to find an answer to the question whether there are health risks associated with the use of mobile phones based on scientific findings. Regarding the recent Swedish study more results have been published that further refute the critique by Boice and McLaughlin (24,25).

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