SECTION 11

Use of Wireless Phones and Evidence for Increased Risk of Brain Tumors

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I. INTRODUCTION

In May 2011 the International Agency for Research on Cancer (IARC) at WHO categorised the radiofrequency electromagnetic fields (RF-EMF) from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields, as a Group 2B, i.e. a 'possible', human carcinogen (Baan et al., 2011, IARC, 2011). Nine years earlier IARC had also classified extremely low frequency (ELF) magnetic field as Group 2B carcinogen (IARC, 2002).

The IARC decision on mobile phones was based mainly on case-control studies from the Hardell group in Sweden and the IARC Interphone study. Both provided supportive results on positive associations between two types of brain tumors; glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones.

The final IARC decision was confirmed by voting of 29 scientists (one not present during voting) at the meeting. A large majority of participants voted to classify RF-EMF radiation as 'possibly carcinogenic' to humans, Group 2B. The decision was also based on occupational studies. We present in this paper an updated review of evidence of the association between use of wireless phones and brain tumors including also papers published after the IARC evaluation.

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

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 1800 MHz, started to operate in 1991 and dominates now the market. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1 900/2 100 MHz RF fields has been introduced worldwide in recent years, in Sweden in 2003. Currently the fourth generation, 4G (Terrestrial 3G), operating at 800/2600 MHz and Trunked Radio Communication (TETRA 380-400 MHz) are being established in Europe. Nowadays mobile phones are used more than landline phones in Sweden (http://www.pts.se/upload/Rapporter/Tele/2011/sv-telemarknad-halvar-2011-pts-er-2011-21.pdf). Worldwide, an estimate of 5.9 billion mobile phone subscriptions was reported at the

end of 2011 by the International Telecommunication Union (ITU; http://www.itu.int/ITU-D/ict/facts/2011/material/ICTFactsFigures2011.pdf).

Desktop cordless phones (DECT) have been used in Sweden since 1988, first using analogue 800-900 MHz RF fields, but since early 1990s using a digital 1900 MHz system. These cordless phones are becoming more common than traditional landlines. They emit RF-EMF radiation similar to that of mobile phones. Thus when human health risks are evaluated it is also necessary to consider the use of cordless phones along with mobile phones.

The real increase in use and exposure to radiation fields from wireless phones (mobile phones and cordless phones) in most countries has occurred since the end of the 1990s. The brain is the main target organ during use of the handheld phone (Cardis et al., 2008). Fear of an increased risk for brain tumors has dominated the debate during the last one or two decades. While RF-EMFs do not have sufficient energy to break chemical bonds like ionising radiation, at least not directly, they can nevertheless have harmful effects on biological tissues. Plausible biological mechanisms for these effects include DNA damage, impairment of DNA repair mechanisms, and epigenetic changes to DNA (see also chapters by H. Lai (Genotoxicity) and I. Belyaev (Physical and Biological Mechanisms).

Primary brain tumors (central nervous system; CNS) constitute of a heterogeneous group of neoplasms of different histological types depending on tissue of origin with different growth patterns, molecular markers, anatomical localisations, and age and gender distributions. The clinical appearance, treatment and prognosis are quite different depending on tumor type.

There are few established risk factors for brain tumors besides ionising radiation (Preston Martin et al., 2006). Higher socio-economic status tends to be related to higher incidence and some rare inherited cancer syndromes account for a small fraction of tumors (Preston Martin et al., 2006). Familial aggregation of glioma has also been reported (Scheurer et al., 2010).

We base this review primarily on the Hardell group papers and the WHO Interphone study (Interphone Study Group, 2010, 2011, Cardis et al., 2011). More discussion of the results and responses, agreements and disagreements of the findings for the Hardell group and Interphone studies can be found in Hardell et al., (2012, 2013).

II. MATERIALS AND METHODS

The PubMed database (www.ncbi.nlm.nih.gov) was used for an up-dated search of published studies in this area using mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. Personal knowledge of published studies was also used in order to get as up-to-date review as possible.

III. RESULTS

Brain tumors overall

Exposure to the radiation from the phones is generally higher in the temporal lobe, the part of the brain that is near to the ear (Cardis et al., 2008). For tumors located in the temporal, occipital or temporoparietal lobe areas of the brain an increased risk was found for ipsilateral exposure, that is the telephone was mostly used on the same side of the head as the tumor appeared, yielding OR = 2.42, 95 % CI = 0.97-6.05 (Hardell et al., 2001). This was the first study in the world that indicated an association between use of mobile phones and an increased risk for brain tumors. However, the results were based on low numbers of exposed subjects and different histopathological types of brain tumors so no firm conclusions could be drawn. Furthermore, this first study did not include use of cordless phones, see also Hardell et al., (1999).

Glioma

Glioma is the most common malignant brain tumor and represents about 60 % of all central nervous system tumors. The most common glioma subtype is astrocytoma. Astrocytic tumors are divided in two groups depending on the malignant potential; low-grade (WHO grades I-II) and high-grade (WHO grades III-IV). Low-grade astrocytoma has a relatively favourable prognosis, whereas survival is shorter for patients with high-grade glioma. Glioblastoma multiforme (WHO grade IV) accounts for 60-75 % of all astrocytoma.

The Hardell group in Sweden studied the association between use of mobile and cordless phones and brain tumors diagnosed during 1997-2003. First, cases diagnosed during 1 January 1997 to 30 June 2000 were included (Hardell et al., 2002, 2003). The next study period included 1 July 2000 to 31 December 2003 (Hardell et al., 2005, 2006a). The methods were the same with the same inclusion criteria and an identical questionnaire in both studies.

In short, both men and women aged 20-80 years at the time of diagnosis were included and all were alive at the time of inclusion in the study. They were reported from cancer registries and had all a brain tumor verified by histopathology. The Swedish Population Registry was used for identification of matched controls. In addition to other exposures use of wireless phones was carefully assessed by a self-administered questionnaire supplemented over the phone. The ear that had mostly been used during calls with mobile phone and/or cordless phone was assessed by separate questions. This information was checked during the supplementary phone calls and finally also by a separate letter with good agreement between these three methods.

Use of the wireless phone was defined as ipsilateral ($\geq$ 50 % of the time), or contralateral (< 50 % of the time) in relation to tumor side. The matched control was assigned the same side as the tumor of the respective case. Use of hands free devices was also assessed as well as use in a car with external antenna. Such use was not included in the calculation of cumulative number of hours for life time use. Latency time was defined as the period from the year of first use until diagnosis (corresponding year for the matched control).

Medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI) were used to define tumor localisation in the brain. Further details can be found in the publications.

As a response to a critique from Boice and McLaughlin (2002) that the exclusion of deceased cases was a source of bias in our studies we performed a study on the cases with a malignant brain tumor that had died before inclusion in the case-control studies 1997-2003. These cases represented patients with a poor prognosis, mostly with astrocytoma WHO grade IV (glioblastoma multiforme). Controls were selected from the Death Registry in Sweden. The study encompassed 464 cases and 464 controls that had died from a malignant disease and 463 controls with other causes of death. Exposure was assessed by a questionnaire sent to the next of kin to each deceased case and control. The questionnaire was similar as in previous studies. This investigation confirmed the previous results of an association between use of mobile phones and malignant brain tumors (Hardell et al., 2010).

We have previously published pooled analysis of malignant brain tumors diagnosed during the period 1997-2003 (Hardell et al., 2006b). These results were updated including also results for the deceased cases with malignant brain tumors (Hardell et al., 2011a, Carlberg, Hardell 2012). The results on use of wireless phones were based on 1,251 cases with malignant brain tumor (response rate 85%) and 2,438 controls (response rate 84%). Most cases had glioma (n=1,148) so we present in the following results for that type of tumor. Latency was divided in three categories, >1-5 years, >5-10 years, and > 10 years from first use of a wireless phone until diagnosis of glioma.

Both use of mobile and cordless phone gave an increased risk overall, highest in the latency group >10 years, increasing further for ipsilateral use yielding for mobile phone OR = 2.9, 95 % CI = 1.8-4.7 and for cordless phone OR = 3.8, 95 % CI = 1.8-8.1 (Table 1). Highest ORs were found in the > 10 year latency group for total wireless phone use as well, OR = 2.1, 95 % CI = 1.6-2.8.
OR increased statistically significant for glioma for cumulative use of wireless phones per 100 h; OR = 1.014, 95 % CI = 1.008-1.019, and per year of latency; OR = 1.056, 95 % CI = 1.037-1.075 (Carlberg and Hardell, 2012). Separate calculations of mobile phone and cordless phone use yielded similar results with statistically significant increasing risks.

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004 under the guidance of IARC. An increased risk for brain tumor was found in some separate country studies and decreased risk in other studies as we have discussed elsewhere (Hardell et al., 2008, 2009). After several years of delay the overall Interphone results were finally published in May 2010 (Interphone Study Group, 2010).

In total 4,301 glioma cases were included in Interphone and the final results were based on 2,708 participating cases (response rate 64 %, range by centre 36-92 %). In total 14,354 potential controls were identified and interviews were completed with 7,658 (53 %, range 42-74 %). The low participation rates in some centres may have created selection bias, see Hardell et al., (2008).

Regular use of mobile phone in the past $\geq$ 1 year gave for glioma OR = 0.81, 95 % CI = 0.70-0.94 (Table 1). Subgroup analyses showed statistically significant increased risk in the highest

exposure group, i.e. those with cumulative mobile phone use ≥ 1,640 hours, OR = 1.40, 95 % CI = 1.03-1.89. The risk increased further for glioma in the temporal lobe yielding OR = 1.87, 95 % CI = 1.09-3.22. In the same exposure category, cumulative use ≥ 1,640 hours and ipsilateral exposure produced OR = 1.96, 95 % CI = 1.22-3.16 in total (no data given for temporal lobe).

In Appendix 2 (Interphone Study Group, 2010, available on the web) analysis was restricted to ever-regular users of mobile phones. Cumulative call time ≥ 1,640 hours gave OR = 1.82, 95 % CI = 1.15-2.89 compared with use < 5 hours. Time since start of regular use (latency) ≥ 10 years produced OR = 2.18, 95 % CI = 1.43-3.31; reference entity 1-1.9 years.

The Interphone study group concluded: "*However, biases and errors limit the strength of the conclusions we can draw from these analyses and prevent a causal interpretation.*" In an editorial accompanying the Interphone results the main conclusion of the Interphone results was described as "*both elegant and oracular…(which) tolerates diametrically opposite readings"* (Saracci and Samet 2010). Several methodological reasons why the Interphone results were likely to have underestimated the risks were discussed including the short latency period since first exposures became widespread; less than 10 % of the Interphone cases had more than 10 years exposure. "*None of the today's established carcinogens, including tobacco, could have been firmly identified as increasing risk in the first 10 years or so since first exposure"*.

Estimated RF-EMF dose in the tumor area from mobile phone use was associated with an increased risk of glioma in parts of the Interphone study (Cardis et al., 2011). OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumor centre for more than 7 years before diagnosis giving OR = 1.91, 95 % CI = 1.05-3.47 (p trend = 0.01) in the highest quintile of exposure. A similar study based on less clear methods was later published by another part of the Interphone study group (Larjavaara et al., 2011). The results seemed not to support the findings of Cardis et al., (2011). However, only 42 cases had used a mobile phone for more than 10 years and no analysis was made of the most exposed group with longest duration of use.

Based on Hardell et al (2011b) and Interphone Study Group (2010) we made meta-analysis of glioma and use of mobile phones. Random-effects model was used based on test for heterogeneity in the overall (≥10 years and ≥1,640 hours) groups. We used published results in

Interphone since we do not have access to their database. Our results were recalculated to these groups of exposure. The meta-analysis yielded for mobile phone use OR = 1.71, 95 % CI = 1.04-2.81 for glioma in the temporal lobe in the ≥ 10 years latency group. Ipsilateral mobile phone use ≥ 1,640 h in total gave the highest risk, OR = 2.29, 95 % CI = 1.56-3.37 (Hardell et al 2012). This meta-analysis strengthens a causal association between use of mobile phones and glioma.

Meningioma

Meningioma is the most common benign brain tumor. It develops from the pia and arachnoid that covers the central nervous system. Meningioma is an encapsulated and well-demarked tumor more common in women than in men. It is rarely malignant.

A pooled analysis of benign brain tumors from the two case-control studies from the Hardell group as discussed above (Hardell et at., 2006c, Hardell and Carlberg, 2009) gave regarding meningioma and use of mobile phone OR = 1.1, 95 % CI = 0.9-1.3, and cordless phone OR = 1.1, 95 % CI = 0.9-1.4 (Table 2). Using > 10 year latency period OR increased; for mobile phone to OR = 1.5, 95 % CI = 0.98-2.4, and for cordless phone to OR = 1.8, 95 % CI = 1.01-3.2. Ipsilateral mobile phone use in the > 10 years latency group yielded OR = 1.6, 95 % CI = 0.9-2.9, and cordless phone OR = 3.0, 95 % CI = 1.3-7.2. These results were based on rather low numbers of exposed cases, however.

Regular use of mobile phone produced in the Interphone study (2010) a statistically significant decreased risk for meningioma, OR = 0.79, 95 % CI = 0.68-0.91, Table 2. The risk increased somewhat with cumulative use ≥ 1,640 hours and ipsilateral mobile phone use to OR = 1.45, 95 % CI = 0.80-2.61. Analysis restricted to tumors in the temporal lobe or to the group of ever-regular use did not change the overall pattern of no increased risk.

We performed meta-analysis of meningioma for use of mobile phone based on results in the Hardell group and Interphone results similarly as for glioma. No statistically significant decreased or increased risk was found (Hardell et al., 2012). These results support the conclusion that up to latency ≥ 10 years or cumulative use ≥1,640 hours there is no consistent pattern of an association between use of mobile phones and meningioma.

Acoustic neuroma

Acoustic neuroma or Vestibular Schwannoma is a slow growing benign tumor located in the eighth cranial nerve in the auditory canal. It grows gradually out into the cerebellopontine angle with potential compression of vital brain stem centres. Tinnitus and hearing problems are usual first symptoms of acoustic neuroma. The eighth cranial nerve is located close to the handheld wireless phone when used, so there is particular concern of an increased risk for neuroma development due to exposure to EMF-RF emissions during use of these devices.

The pooled analysis of the Hardell group studies yielded regarding use of mobile phones for acoustic neuroma OR = 1.7, 95 % CI = 1.2-2.3 increasing to OR = 2.9, 95 % CI = 1.6-5.5 with > 10 years latency period, Table 3. Ipsilateral use increased the risk further; in the > 10 years latency group to OR = 3.0, 95 % CI = 1.4-4.2 (Hardell and Carlberg, 2009). Cordless phone use gave OR = 1.5, 95 % CI = 1.04-2.0 increasing to OR = 1.7, 95 % CI =1.2-2.5 for ipsilateral use in the > 1 year latency group.

In the Interphone study (2011) 1,121 (82 %) acoustic neuroma cases participated, range 70-100 % by centre. Of the controls 7,658 (53 %) completed the interviews, range 35-74 % by centre. The final matched analysis (1:1 or 1:2) consisted of 1,105 cases and 2,145 controls. Overall no increased risk was found censoring exposure at one year or at 5 years before reference date, OR = 0.85, 95 % CI = 0.69-1.04 and OR = 0.95, 95 % CI = 0.77-1.17, respectively (Table 3).

Cumulative number of hours of ipsilateral mobile phone use $\geq$ 1,640 hours up to 1 year before reference date gave OR = 2.33, 95 % CI = 1.23-4.40 and contralateral use OR = 0.72, 95 % CI = 0.34-1.53 for acoustic neuroma, see Table 3 (Interphone Study Group, 2011). For cumulative number of hours of ipsilateral mobile phone use $\geq$ 1,640 hours up to 5 years before reference date OR = 3.53, 95 % CI = 1.59-7.82, and for contralateral use OR = 1.69, 95 % CI = 0.43-6.69 were obtained. The risk increased further for cumulative ipsilateral use $\geq$ 1,640 hours with start $\geq$ 10 years before reference date to OR = 3.74, 95 % CI = 1.58-8.83. Contralateral use in that group yielded OR = 0.48, 95 % CI = 0.12-1.94, however based on only 4 exposed cases and 9 exposed controls. Overall OR = 1.93, 95 % CI = 1.10-3.38 was obtained for long-term use with start $\geq$ 10 years before reference date and cumulative call time $\geq$ 1,640 hours.

Similar analyses of the data as in Appendix 2 for glioma (see Interphone Study Group, 2010) yielded highest OR for acoustic neuroma in the shortest latency group, 2-4 years before reference date, OR = 1.41, 95 % CI = 0.82-2.40. Lower OR was calculated in the ≥ 10 years group, OR = 1.08, 95 % CI = 0.58-2.04. Somewhat higher risk than in total, OR = 1.32, 95 % CI = 0.88-1.97, was found for cumulative mobile phone use ≥ 1,640 hours; OR = 1.74, 95 % CI = 0.90-3.36, in this analysis restricted to only regular users. No results were given for ipsilateral use.

We performed meta-analysis of the results for use of mobile phone and the association with acoustic neuroma based on results by the Hardell group and Interphone study (Hardell et al 2012). For the latency group ≥ 10 years highest risk was obtained for ipsilateral use, OR = 1.81, 95 % CI = 0.73-4.45. The risk increased further for cumulative use ≥ 1,640 hours yielding OR = 2.55, 95 % CI = 1.50-4.40 for ipsilateral use. The meta-analysis strengthens a causal association between use of mobile phones and acoustic neuroma.

A case-case study was performed in Japan (Sato et al., 2011). The cases were identified during 2000-2006 at 22 participating neurosurgery departments. The diagnosis was based on histopathology or CT/MRI imaging. Of 1,589 cases 816 (51 %) agreed to participate and answered a mailed questionnaire. The final analysis included 787 cases, Cases with ipsilateral use were regarded as exposed and those with contralateral use were assumed to be unexposed and were used as the reference category. Overall no increased risk was found. However, for average daily call duration > 20 minutes with reference date 1 year Risk Ratio (RR) = 2.74, 95 % CI = 1.18-7.85 was found increasing to OR = 3.08, 95 % CI = 1.47-7.41 with reference date 5 years before diagnosis (Table 3). Unfortunately no results were given for cumulative number of hours for use over the years. For cordless phones no increased risk was found but the analysis was not very informative.

Risks to children and adolescents

The developing brain is more sensitive to toxins (Kheifets et al., 2005) and it is still developing until about 20 years of age (Dosenbach et al., 2010). Children have smaller head and thinner skull bone than adults. Their brain tissue has also higher conductivity and these circumstances give higher absorption from RF-EMF than for adults (Cardis et al., 2008, Christ et al., 2010, Gandhi et al., 2012). Use of wireless phones is widespread among children and adolescents

(Söderqvist et al., 2007, 2008). The greater absorption of RF energy per unit of time, the greater sensitivity of their brains, and their longer lifetimes with the risk to develop a brain tumor leaves children at a higher risk than adults from mobile phone radiation.

We have published results regarding brain tumor risk for different age groups at the time of diagnosis (Hardell et al., 2004) or age at first use of wireless phones (Hardell and Carlberg, 2009, Hardell et al., 2011a, 2012, 2013). Three age groups for first use of a wireless phone were used: <20 years, 20-49 years and 50-80 years. Highest risk for glioma was found for first use of mobile phone or cordless phone before the age of 20 years (Table 4). Thus, mobile phone use yielded for glioma OR = 3.1, 95 % CI = 1.4-6.7 and cordless phone OR 2.6, 95 % CI = 1.2-5.5.

Also for acoustic neuroma the risk was highest in the youngest age group with OR = 5.0, 95 % CI = 1.5-16 for use of mobile phone. Only one case had first use of cordless phone before the age of 20, so no conclusions could be drawn for cordless phones. Regarding meningioma no clear pattern of age-dependent increased risk was seen.

A multi-centre case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO (Aydin et al., 2011). It included children and adolescents aged 7–19 years and has been commented elsewhere in detail since serious methodological problems exist in the study design and interpretation of the results (Söderqvist et al., 2011). In CEFALO a statistically non-significant increased risk for brain tumors among regular users (one call per week for at least 6 months) of mobile phones was found; OR = 1.36, 95 % CI = 0.92-2.02. This OR increased somewhat with cumulative duration of subscriptions and duration of calls (Aydin et al., 2011). No data for long-term use were given; the longest latency period was 5 years. Further support of a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for time since first subscription >2.8 years yielded a statistically significant OR of 2.15, 95 % CI = 1.07-4.29, with a statistically significant trend (p=0.001).

Use of cordless phones was covered only in the first 3 years of use. No explanation was given for this most peculiar definition. Wireless phone use was not considered, that is use of both mobile phones and cordless phones as the relevant exposure category, as used by the Hardell group and adopted by IARC (Baan et al., 2011). Instead Aydin et al., (2011) included use of

cordless phones in the 'unexposed' category when risk estimates were calculated for mobile phone use. Similarly, regarding use of cordless phones RF-EMF emissions from mobile phones were regarded as 'no exposure'. Thus, an increased risk was potentially concealed.

The authors summarised that they "*did not observe that regular use of a mobile phone increased the risk for brain tumors*." An editorial in the same journal accompanied that conclusion by stating by that the study showed "*no increased risk of brain tumors*" (Boice and Tarone, 2011). This was echoed by a news release from the Karolinska Institute in Stockholm claiming that the results of no increased risk were 'reassuring' (Karolinska Institute, 2011). However the results indicate a moderately increased risk, in spite of low exposure, short latency period and limitations in study design and analyses. Certainly it cannot be used as reassuring evidence against an association, see Söderqvist et al., (2011).

Danish cohort study on mobile phone subscribers

An attempt to establish a cohort of mobile phone users was made in Denmark in co-operation between the Danish Cancer Society and the International Epidemiology Institute (IEI), Rockville, MD, USA. It was financed by grants from two Danish telecom operation companies (TeleDenmark Mobil and Sonafon), IEI, and the Danish Cancer Society. The source of money for IEI has not been disclosed.

The Danish study on brain tumor risk among mobile phone subscribers has so far resulted in four publications (Johansen et al., 2001, Schüz et al., 2006, Frei et al., 2011, Schüz et al., 2011). It included subjects from January 1, 1982 until December 31, 1995 identified from the computerised files of the two Danish operating companies, TeleDenmark Mobil and Sonofon. A total of 723,421 subscribers were initially identified but the final cohort consisted of only 58 % of these subjects. Due to lack of names of individual users 200,507 corporate users were excluded.

We have discussed elsewhere several shortcomings in the Danish cohort study such as exclusion of corporate users, no individual exposure data, users of cordless phones are included in the reference category, no control for use of mobile phones in the population after the establishment of the cohort, and no operator-verified data on years of subscription is available (Söderqvist et al., 2012). These limitations are likely to have led to an underestimate of any risk in this study.

One would also expect considerable misclassification of mobile phone use both among subscribers and the reference population since no new subscribers were included in the exposed cohort after 1995.

The IARC working group concluded that the methods used could have resulted in considerable misclassification in exposure assessment in the Danish cohort study on mobile phone subscribers (Baan et al., 2011).

After the outcome of the IARC-evaluation was made public in June 2011 (Baan et al., 2011) two additional reports on the Danish cohort were published (Frei et al., 2011, Schüz et al., 2011). Both were new up-dates of the initial cohort and included more information on risk related to longer follow-up. One focused on acoustic neuroma (Schüz et al., 2011) while the other gave results both for all cancers and separately for glioma and meningioma (Frei et al., 2011). This time the number of the cohort was reduced to 358,403 (49.5 %) of the initially identified subscribers (n=723,421). The major additional exclusion (n=54,350) was due to record linkage with the Danish so-called CANULI cohort on socioeconomic factors (Dalton et al., 2008).

The authors of the Danish study have themselves pointed out the main causes of considerable exposure misclassifications (Frei et al., 2011). While at least non-response and recall bias can be excluded the study has serious limitations related to exposure assessment (Söderqvist et al., 2012). In fact, these limitations cloud the findings of the four reports to such an extent they are uninformative at best. At worst, they may be used in a seemingly solid argument against an increased risk; as reassuring results from a large nationwide cohort study.

Brain tumor incidence

It has been suggested that overall incidence data on brain tumors for countries show no increasing trends and may be used to disqualify the association between mobile phone use and brain tumors observed in the case-control studies (Aydin et al., 2011; Ahlbom, and Feychting, 2011; Deltour et al., 2012; Little et al., 2012).

However, by now several studies show increasing incidence of brain tumors. In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system

tumors (combined) was seen during 2000-2009; in men +2.7 %, 95 % CI = +1.1 to 4.3 % and in women +2.9 %, 95 % CI = +0.7 to 5.2 % (NORDCAN). Updated results for brain and central nervous system tumors have been released in Denmark. The age-standardized incidence of brain and central nervous system tumors increased with 40 % among men and 29 % among women during 2001-2010 (Sundhedsstyrelsen, 2010). A more recent news release based on the Danish Cancer Register stated that during the last 10 years there has been an increasing number of cases with the most malignant glioma type, glioblastoma multiforme (astrocytoma WHO grade IV), especially among men (http://www.cancer.dk/Nyheder/nyhedsartikler/2012kv4/Kraftig+stigning+i+hjernesvulster.htm).

Little et al., (2012) studied the incidence rates of glioma during 1992-2008 in the United States and compared with ORs for glioma associated with mobile phone use in the 2010 Interphone publication (Interphone Study Group, 2010) and our pooled results published in 2011 (Hardell et al., 2011a). Since our results are discussed and questioned by Little et al their study needs to be reviewed in more detail. Our response to the journal (BMJ) was never accepted for publication in the journal and cannot be found via PubMed, only on the web (http://www.bmj.com/content/344/bmj.e1147/rr/578564).

First, one important methodological issue that was not stated in the abstract or in the article [Figures 2-4] by Little et al., (2012), but can be found in the web appendix, is that observed rates were based on men aged 60-64 years from the Los Angeles SEER registry as the baseline category. These data were used to estimate rates in the entire dataset, men and women aged $\geq$ 18 years and all 12 SEER registries. Thereby numerous assumptions were made as pointed out by Kundi (2012) and Davis et al., (2012).

Using only men, as Little et al., did, ignores the fact that women had less frequent use of mobile phones than men in our studies (Table 5). Overall 31 % of women reported such use *versus* 57 % of men. Furthermore, use varies with age group with a large difference according to age, as we have explored in our publications (Hardell and Carlberg, 2009, Hardell et al., 2011a). Thus, the age group 60-64 year old men is not valid to use for these calculations.

There are several other points that may be added. Another example is that the results for anatomical localisations and tumor grade [in Table 5 in the article] by Little et al are based on numerous assumptions from SEER data, Interphone and the Hardell group studies. The authors seem not to have paid attention to the fact that the fraction of mobile phone users differs for gender and age, see Table 5.

One interesting result that was not commented further by Little et al., (2012) was the finding of a statistically significant yearly increasing incidence of high-grade glioma (WHO grades III-IV) in the SEER data for 1992-2008, +0.64%, 95% CI = +0.33 to 0.95 %. On the contrary, the incidence of low-grade glioma (WHO grades I-II) decreased with –3.02 %, 95 % CI = –3.49 to –2.54 %. Little et al., (2012) found also a statistically significant increasing yearly trend for glioma in the temporal lobe, +0.73 %, 95 % CI = +0.23 to 1.23 %.

Zada et al., (2012) studied incidence trends of primary malignant brain tumors in the Los Angeles area during 1992-2006. The overall incidence of primary malignant brain tumors decreased over the time period with the exception of glioblastoma multiforme (astrocytoma WHO grade IV). The annual age adjusted incidence rate of that tumor type increased statistically significant in the frontal lobe with Annual Percentage Change (APC) +2.4 % to +3.0 % ($p \leq 0.001$) and temporal lobe APC +1.3 % to +2.3 % ($p \leq 0.027$) across all registries. In the California Cancer Registry the incidence of glioblastoma multiforme increased also in cerebellum, APC +11.9 % ($p < 0.001$). For lower grade astrocytoma decreases of annual age adjusted incidence rates were observed. The authors concluded that there was a real increase in the incidence of glioblastoma multiforme in frontal and temporal lobes and cerebellum, areas of the brain with the highest absorbed dose of RF-EMF emissions from handheld mobile phones (Cardis et al., 2008).

Of interest is also the report by de Vocht et al., (2011) from England that showed for the time period 1998 to 2007 a statistically significant increasing incidence of brain tumors, the majority glioma, in the temporal lobe for men and women ($p < 0.01$), and frontal lobe for men ($p < 0.01$). The incidence increased also for women in the frontal lobe, although not statistically significant ($p = 0.07$). The incidence decreased in other parts of the brain.

Deltour et al., (2012) reported increasing glioma incidence rates in Denmark, Finland, Norway, and Sweden for the time period 1979-2008. APC increased for men with +0.4 %, 95 % CI +0.1 to 0.6 % and for women with +0.3 %, 95 % CI +0.1 to 0.5 %. A study from Australia for the time period 2000-2008 showed that APC for malignant brain tumors increased statistically significant +3.9 %, 95 % CI +2.4 to 5.4 % (Dobes et al., 2011). An increase was seen among both men and women. The APC for benign tumors increased with +1.7 %, 95 % CI -1.4 to +4.9 %, thus not statistically significant.

From urban Shanghai an increasing incidence of brain and nervous system tumors for the time period 1983-2007 was reported with APC +1.2 %, 95 % CI +0.4 to 1.9 % in males and APC +2.8 %, 95 % CI +2.1 to 3.4 % in females (Ding and Wang, 2011).

We reported increasing incidence of astrocytoma WHO grades I-IV during 1970-2007 in Sweden. In the age group > 19 years the annual change was +2.16 %, 95 % CI +0.25 to 4.10 % during 2000-2007, for further details see Hardell and Carlberg (2009).

IV. DISCUSSION

As pointed out by IARC (Baan et al., 2011) the most comprehensive results on use of wireless phones and the association with brain tumors come from the Hardell group in Sweden and the international Interphone study. Results for latency time of 10 years or more have been published from both study groups.

Both were case-control studies and the cases were recruited during similar time periods, 1997-2003 in the Hardell group and during 2000-2004 in Interphone, with somewhat different years in the varying study regions. There was no overlapping of cases in the Hardell group studies and the Swedish part of Interphone.

The Hardell group included cases aged 20-80 years whereas eligible cases in Interphone were aged 30-59 years at diagnosis. One control subject matched on age, gender and geographical area (region) to each case in the Hardell group studies was drawn from the national population register. In Interphone one control was selected for each case from a ‘locally appropriate population-based sampling frame’. In Germany two controls were selected and the centres used

individual matching or frequency matching. Regarding the Interphone study on acoustic neuroma some centres sampled special controls to the cases, other draw controls from the pool of controls in the glioma and meningioma studies, or used a mixture of both methods. In UK general practioners' lists (Hepworth et al 2006) and in Japan random digit dialling were used (Takebayashi et al., 2006, 2008). Certainly the methods used in Interphone may introduce selection bias.

Use of wireless phones and other exposures were carefully assessed by a self-administered questionnaire in the Hardell et al., studies. The information was supplemented over the phone by trained interviewers thereby using a structured protocol. This was done blinded as to case or control status. After the interviews all personal data like names and addresses were removed from the questionnaires so that only an id-number that did not disclose if it was a case or a control was shown. Thus, coding of the data for statistical analysis was performed without personal data of the individual.

On the contrary information on past mobile phone use was collected during face-to-face interviews in Interphone obviously disclosing if it was a case or a control that was interviewed. These interviews were performed by a large number of interviewers at different participating centres. Experienced interviewers were defined as those who conducted at least 20 interviews. In fact, in the sensitivity analysis the risk increased for glioma for cumulative mobile phone use $\geq$ 1,640 hours from OR = 1.40, 95 % CI 1.03-1.89 to OR = 1.50, 95 % CI = 1.10-2.06 if 'experienced interviewers only' were considered. The higher risk restricting analysis to 'experienced interviewers' in Interphone indicates observational bias during assessment of exposure decreasing the risk.

In the Hardell group studies few persons conducted all interviews of the 1,251 participating cases with malignant brain tumor, 1,254 cases with benign brain tumor, and 2,438 controls (total 4,942; note one case had both a malignant and a benign brain tumor). All interviewers were first educated; they used a defined protocol and gained considerable experience as interviewers. In fact, they were obliged to carry out the interviews extensively to fulfil the quality in data assessment according to the structured protocol. It is obvious that the few interviewers in the Hardell group study must have been much more experienced than the diversity of interviewers in Interphone.

In the personal interviews in Interphone a computer program that guided the interview with questions read by the interviewer from a laptop computer screen was used. The answers were entered directly into the computer by the interviewer. Using computer based face-to-face interviews may be a stressful situation for the patients. In fact patients scored significantly lower than controls due to recalling of words (aphasia), problems with writing and drawing due to paralysis in the Danish part of Interphone (Christensen et al., 2005). Furthermore, it has not been disclosed how the personal interviews were performed in sparsely populated areas, e.g. in the Northern Sweden. Did the interviewers travel long distances for interviews of controls in rural areas or were all controls living in the largest cities thereby creating selection bias?

In the Hardell group studies the response rate was 85 % (n=1,251) for cases with malignant brain tumor, 88 % (n=1,254) for cases with benign brain tumor, and 84 % (n=2,438) for controls (Hardell et al., 2006c, Carlberg and Hardell, 2012). Lower response rates were obtained in Interphone study, 64 %, range by centre 36-92 %, (n=2,765) for glioma cases, 78 %, range 56-92 %, (n=2,425) for meningioma cases, 82 %, range 70-100 % (n=1,121) for acoustic neuroma cases, and 53 %, range 42-74 %, (n=7,658) for controls (Interphone Study Group, 2010; 2011). These low response rates may have created the possibility of considerable selection bias (Hardell et al., 2008). Not responding controls in Interphone tended to be less frequent users of mobile phone than participating controls leading to underestimation of the risk.

The Hardell group studies included subjects aged 20-80 years, versus 30-59 years in Interphone. We have shown that restricting the age group to 30-59 years and considering subjects that used a cordless phone as unexposed in the Hardell group studies reduced the ORs and produced results quite similar to Interphone (Hardell et al., 2011b). Latency time > 10 years for glioma in the temporal lobe yielded OR = 1.40, 95 % CI = 0.70-2.81 in the Hardell group studies and OR = 1.36, 95 % CI = 0.88-2.11 in Interphone (latency $\geq$ 10 years). Thus, excluding exposure to RF-EMFs from cordless phones as in the Interphone study as well as excluding the younger and older subjects biased the ORs towards unity in Interphone, which likely dilutes the ability to see health risks.

By placing a strong emphasis on incidence data an association between use of wireless phones and brain tumors has been challenged (Swerdlow et al., 2011). The authors considered that if the

increased risks seen in case-control studies reflect a causal relationship, there would already be an increase in incidence of brain and central nervous system tumors. As discussed above by now increasing incidence rates, especially for certain brain tumor types and anatomical localisations of relevance, have been reported. The natural history of most glioma from earliest events to clinical manifestation is unknown, but most likely several decades. The exposure duration in most studies is thus incompatible with a tumor initiating effect. If the exposure on the other hand acts as a promoter, this would decrease latency time for already existing tumors, giving a temporary but not a continuous increase in incidence (Kundi, 2010).

The first case in the world on worker's compensation for a brain tumor after long-term use of wireless phones was the ruling 12 October 2012 by the Italian Supreme Court. A previous ruling that the Insurance Body for Work (INAIL) must grant compensation to a businessman who had used wireless phones for 12 years and developed a neurinoma in the brain was affirmed (http://www.applelettrosmog.it/public/news.php?id_news=44 ; www.microwavenews.com). He had used both mobile and cordless phones for five to six hours per day preferably on the same side as the tumour developed. The neurinoma was located in the trigeminal Gasser's ganglion in the brain. This 5th cranial nerve controls facial sensations and muscles. It is the same type of tumour as the acoustic neuroma in the 8th cranial nerve located in the same area of the brain. No further appeal of the Supreme Court decision is possible.

V. CONCLUSIONS

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

In summary:

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

Authors' contributions

Lennart Hardell was responsible for drafting of the manuscript and Michael Carlberg made all statistical calculations. Michael Carlberg and Kjell Hansson Mild read and gave valuable comments on the manuscript. All authors have read and approved the final version. No conflicts of interest reported. Supported by grants from Cancer- och Allergifonden, Cancerhjälpen, and Örebro University Hospital Cancer Fund.

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Table 1. Summary of studies on the use of wireless phones and glioma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006b, 2010, 2011a) Carlberg, Hardell (2012) Sweden	1997-2003 Case-control	20-80 years	Glioma (n=1148)	123	OR **2.5** (1.8-3.3)	>10 year latency, mobile phone
				57	OR **2.9** (1.8-4.7)	>10 year latency, mobile phone, *ipsilateral*, only living
				50	OR **2.6** (1.7-4.1)	>10 year latency, *mobile phone only*
				45	OR **1.7** (1.1-2.6)	>10 year latency, cordless phone
				20	OR **3.8** (1.8-8.1)	>10 year latency, cordless phone, *ipsilateral*, only living
				9	OR 1.2 (0.5-2.9)	>10 year latency, *cordless phone only;* >5-10 year latency OR **1.9** (1.3-2.9; n=55)
				150	OR **2.1** (1.6-2.8)	>10 year latency, wireless phone (mobile and cordless phone)
			Astrocytoma, high grade (n=820)	102	OR **3.0** (2.1-4.2)	>10 year latency, mobile phone
				47	OR **3.9** (2.3-6.6)	>10 year latency, mobile phone, ipsilateral, only living
				37	OR **2.8** (1.7-4.6)	>10 year latency, *mobile phone only*
				36	OR **2.0** (1.2-3.2)	>10 year latency, cordless phone
				15	OR **5.5** (2.3-13)	>10 year latency, cordless phone, ipsilateral, only living
				6	OR 0.9 (0.3-2.6)	>10 year latency, *cordless phone only;* >5-10 year latency OR **2.4** (1.6-3,7; n=44)
				121	OR **2.5** (1.8-3.4)	>10 year latency, wireless phone (mobile and cordless phone)

Table 1. cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone Study Group (2010) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Glioma (n=2708)	1666	OR **0.81** (0.70-0.94)	Regular use of mobile phone in the past ≥1 year
				210	OR **1.40** (1.03-1.89)	Cumulative hours mobile phone ≥ 1640 hours
				78	OR **1.87** (1.09-3.22)	Cumulative hours mobile phone ≥ 1640 hours, tumors in *temporal lobe*
				100	OR **1.96** (1.22-3.16)	Cumulative hours mobile phone ≥ 1640 hours, *ipsilateral* mobile phone use
Interphone Study Group (2010) Appendix 2			Glioma (n=1211)	460	OR **1.68** (1.16-2.41)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				468	OR **1.54** (1.06-2.22)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				190	OR **2.18** (1.43-3.31)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				160	OR **1.82** (1.15-2.89)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 2. Summary of studies on the use of wireless phones and meningioma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006c), Hardell, Carlberg (2009) Sweden	1997-2003 Case-control	20-80 years	Meningioma (n=916)	347	OR 1.1 (0.9-1.3)	> 1 year latency, mobile phone use
				38	OR 1.5 (0.98-2.4)	> 10 years latency of mobile phone use
				18	OR 1.6 (0.9-2.9)	> 10 years latency of ipsilateral mobile phone use
				294	OR 1.1 (0.9-1.4)	> 1 year latency, cordless phone
				23	OR 1.8 (1.01-3.2)	> 10 years latency of cordless phone use
				11	OR **3.0** (1.3-7.2)	> 10 years latency of ipsilateral cordless phone use
Interphone Study Group (2010) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Meningioma (n=2409)	1262	OR **0.79** (0.68-0.91)	Regular use of mobile phone in the past ≥1 year
				130	OR 1.15 (0.81-1.62)	Cumulative hours mobile phone ≥ 1640 hours
				21	OR 0.94 (0.31-2.86)	Cumulative hours mobile phone ≥ 1640 hours, tumors in *temporal lobe*
				46	OR 1.45 (0.80-2.61)	Cumulative hours mobile phone ≥ 1640 hours, *ipsilateral* mobile phone use

Table 2. cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone (2010) Appendix 2	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Meningioma (n=842)	362	OR 0.90 (0.62-1.31)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				288	OR 0.75 (0.51-1.10)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				76	OR 0.86 (0.51-1.43)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				96	OR 1.10 (0.65-1.85)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 3. Summary of studies on the use of wireless phones and acoustic neuroma risk

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Hardell et al (2006c), Hardell, Carlberg (2009) Sweden	1997-2003 Case-control	20-80 years	Acoustic neuroma (n=243)	130	OR **1.7** (1.2-2.3)	> 1 year latency of mobile phone use
				20	OR **2.9** (1.6-5.5)	> 10 years latency of mobile phone use
				13	OR **3.0** (1.4-6.2)	> 10 years of *ipsilateral* mobile phone use
				4	OR 1.3 (0.4-3.8)	> 10 years latency of cordless phone use
				3	OR 2.3 (0.6-8.8)	> 10 years latency of *ipsilateral* cordless phone use
Sato et al (2011) Japan	2000-2006 Case-case	All ages	Acoustic neuroma (n=787)	97	RR 1.08 (0.93-1.28)	Mobile phone, reference date 1 year before diagnosis, *ipsilateral*
				86	RR 1.14 (0.96-1.40)	Mobile phone, reference date 5 years before diagnosis, *ipsilateral*
				18	RR **2.74** (1.18-7.85)	Mobile phone, reference date 1 year before diagnosis, average daily call duration >20 min, *ipsilateral*
				28	RR **3.08** (1.47-7.41)	Mobile phone, reference date 5 years before diagnosis, average daily call duration >20 min, *ipsilateral*
				45	RR 0.93 (0.79-1.14)	Cordless phone, reference date 1 year before diagnosis, *ipsilateral;* mobile phone non-users
				125	RR 1.02 (0.91-1.17)	Cordless phone, reference date 5 years before diagnosis, *ipsilateral;* mobile phone non-users

Table 3 cont.

Study	Years Study Type	Age	Tumour type	No. of exposed cases	Odds ratio, 95 % confidence interval	Comments
Interphone Study Group (2011) 13 countries; Australia, Canada, Denmark, Finland, France, UK, Germany, Israel, Italy, Japan, New Zealand, Norway, Sweden	2000-2004, 2-4 years depending on study region. Case-control	30-59 years	Acoustic neuroma (n=1105)	643	OR 0.85 (0.69-1.04)	Mobile phone regular use up to 1 year before reference date
				304	OR 0.95 (0.77-1.17)	Mobile phone regular use up to 5 years before reference date
				77	OR 1.32 (0.88-1.97)	Cumulative hours mobile phone ≥ 1640 hours up to 1 year before reference date
				36	OR **2.79** (1.51-5.16)	Cumulative hours mobile phone ≥ 1640 hours up to 5 years before reference date
				47	OR **2.33** (1.23-4.40)	Cumulative hours mobile phone ≥ 1640 hours up to 1 year before reference date; *ipsilateral* use
				27	OR **3.53** (1.59-7.82)	Cumulative hours mobile phone ≥ 1640 hours up to 5 years before reference date; *ipsilateral* use
				37	OR **1.93** (1.10-3.38)	Cumulative hours mobile phone ≥ 1640 hours in the past start ≥10 years before reference date
				28	OR **3.74** (1.58-8.83)	Cumulative hours mobile phone ≥ 1640 hours in the past start ≥10 years before reference date, *ipsilateral*
				225	OR 1.41 (0.82-2.40)	Restricted to *ever regular use* time since start 2-4 years; 1-1.9 years as reference entity
				209	OR 1.38 (0.80-2.39)	Restricted to *ever regular use* time since start 5-9 years; 1-1.9 years as reference entity
				64	OR 1.08 (0.58-2.04)	Restricted to *ever regular use* time since start 10+ years; 1-1.9 years as reference entity
				72	OR 1.74 (0.90-3.36)	Restricted to *ever regular use* ≥1640 hours, <5 hours as reference entity

Table 4. Odds ratio (OR) and 95 % confidence interval (CI) for glioma, meningioma and acoustic neuroma in different age groups for first use of the wireless phone (Hardell et al 2006b,c, 2010, 2011a). Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis. For glioma adjustment was also made for vital status.

	Glioma (n=1148)		**Meningioma (n=916)**		**Acoustic neuroma (n=243)**	
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI
Mobile phone	529/963	**1.3** (1.1-1.6)	347/900	1.1 (0.9-1.3)	130/900	**1.7** (1.2-2.3)
< 20 years old	17/14	**3.1** (1.4-6.7)	5/14	1.9 (0.6-5.6)	5/14	**5.0** (1.5-16)
20-49 years old	315/581	**1.4** (1.1-1.7)	210/555	1.3 (0.99-1.6)	86/555	**2.0** (1.3-2.9)
≥ 50 years old	197/368	**1.3** (1.01-1.6)	132/331	1.0 (0.8-1.3)	39/331	1.4 (0.9-2.2)
Cordless phone	402/762	**1.3** (1.1-1.6)	294/701	1.1 (0.9-1.4)	96/701	**1.5** (1.04-2.0)
< 20 years old	16/16	**2.6** (1.2-5.5)	2/16	0.5 (0.1-2.2)	1/16	0.7 (0.1-5.9)
20-49 years old	206/437	1.2 (0.9-1.5)	167/416	1.3 (0.98-1.6)	65/416	**1.7** (1.1-2.5)
≥ 50 years old	180/309	**1.4** (1.1-1.7)	125/269	1.1 (0.8-1.4)	30/269	1.3 (0.8-2.1)

Table 5. Gender and age distribution for use of mobile phones among cases aged 20-80 years in the Hardell group studies. Glioma (n=1148).

	Men		Women		Total	
Age, diagnosis	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones	No use/≤1 year latency, mobile phones	Use >1 year latency, mobile phones
20-24	8	7 (47 %)	3	8 (73 %)	11	15 (58 %)
25-29	10	15 (60 %)	5	10 (67 %)	15	25 (63 %)
30-34	11	26 (70 %)	19	8 (30 %)	30	34 (53 %)
35-39	9	23 (72 %)	8	13 (62 %)	17	36 (68 %)
40-44	10	26 (72 %)	16	11 (41 %)	26	37 (59 %)
45-49	14	37 (73 %)	12	16 (57 %)	26	53 (67 %)
50-54	22	61 (73 %)	26	27 (51 %)	48	88 (65 %)
55-59	35	65 (65 %)	59	20 (25 %)	94	85 (47 %)
60-64	41	51 (55 %)	53	15 (22 %)	94	66 (41 %)
65-69	55	46 (46 %)	57	13 (19 %)	112	59 (35 %)
70-74	43	16 (27 %)	41	5 (11 %)	84	21 (20 %)
75-80	27	8 (23 %)	35	2 (5 %)	62	10 (14 %)
All	**285**	**381 (57 %)**	**334**	**148 (31 %)**	**619**	**529 (46 %)**