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Pathophysiology 20 (2013) 85–110

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# Use of mobile phones and cordless phones is associated with increased risk for glioma and acoustic neuroma

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Received 11 October 2012; received in revised form 14 November 2012; accepted 15 November 2012

**Abstract**

The International Agency for Research on Cancer (IARC) at WHO evaluation of the carcinogenic effect of RF-EMF on humans took place during a 24–31 May 2011 meeting at Lyon in France. The Working Group consisted of 30 scientists and categorised the radiofrequency electromagnetic fields from mobile phones, and from other devices that emit similar non-ionising electromagnetic fields (RF-EMF), as Group 2B, i.e., a 'possible', human carcinogen. The decision on mobile phones was based mainly on the Hardell group of studies from Sweden and the IARC Interphone study. We give an overview of current epidemiological evidence for an increased risk for brain tumours including a meta-analysis of the Hardell group and Interphone results for mobile phone use. Results for cordless phones are lacking in Interphone. The meta-analysis gave for glioma in the most exposed part of the brain, the temporal lobe, odds ratio (OR) = 1.71, 95% confidence interval (CI) = 1.04–2.81 in the ≥10 years (>10 years in the Hardell group) latency group. Ipsilateral mobile phone use ≥1640 h in total gave OR = 2.29, 95% CI = 1.56–3.37. The results for meningioma were OR = 1.25, 95% CI = 0.31–4.98 and OR = 1.35, 95% CI = 0.81–2.23, respectively. Regarding acoustic neuroma ipsilateral mobile phone use in the latency group ≥10 years gave OR = 1.81, 95% CI = 0.73–4.45. For ipsilateral cumulative use ≥1640 h OR = 2.55, 95% CI = 1.50–4.40 was obtained. Also use of cordless phones increased the risk for glioma and acoustic neuroma in the Hardell group studies. Survival of patients with glioma was analysed in the Hardell group studies yielding in the >10 years latency period hazard ratio (HR) = 1.2, 95% CI = 1.002–1.5 for use of wireless phones. This increased HR was based on results for astrocytoma WHO grade IV (glioblastoma multiforme). Decreased HR was found for low-grade astrocytoma, WHO grades I–II, which might be caused by RF-EMF exposure leading to tumour-associated symptoms and earlier detection and surgery with better prognosis. Some studies show increasing incidence of brain tumours whereas other studies do not. It is concluded that one should be careful using incidence data to dismiss results in analytical epidemiology. The IARC carcinogenic classification does not seem to have had any significant impact on governments' perceptions of their responsibilities to protect public health from this widespread source of radiation.


*Keywords:* Brain tumour; Glioma; Meningioma; Acoustic neuroma; Wireless phones; Incidence; Adolescent risk; CEFALO; Danish cohort

## 1. Introduction

On 31 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 [1,2]. Nine years earlier IARC had also classified extremely low frequency (ELF) magnetic field as Group 2B carcinogen [3].

The IARC evaluation of the carcinogenic effect of RF-EMF on humans took place during a 24–31 May 2011 meeting at Lyon in France. The Working Group consisted of 30 scientists representing four areas: 'animal cancer studies', 'epidemiology', 'exposure' and 'mechanistic and other relevant data'. The expert groups initially prepared a written draft prior to the IARC meeting. Further work was done in the expert groups and a final agreement, sentence by sentence, was obtained during plenary sessions with all experts participating.

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http://dx.doi.org/10.1016/j.pathophys.2012.11.001

The IARC decision on mobile phones was based mainly on two sets of case-control human studies; the Hardell group of studies from Sweden and the IARC Interphone study. Both provided complementary and supportive results on positive associations between two types of brain tumours; 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). 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.

In this paper an up-to-date review of the evidence of an association between use of wireless phones and brain tumours is presented. The Nordic countries were among the first countries in the world to widely adopt wireless telecommunications technology. Analogue phones (NMT; Nordic Mobile Telephone System) were introduced in the early 1980s using both 450 and 900 Megahertz (MHz) frequencies. NMT 450 was used in Sweden from 1981 but closed down on 31 December 2007, NMT 900 operated during 1986–2000.

The digital system (GSM; Global System for Mobile Communication) using dual band, 900 and 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 1900/2100 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 Sweden and elsewhere. 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). Many users are children and adolescents, which is of special concern regarding potential health effects.

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. The cordless phones are becoming more common than traditional landlines. Also these phones emit RF-EMF radiation similar to that of mobile phones. Thus, it is also necessary to consider the usage of cordless phones along with mobile phones, when human health risks are evaluated. It should be noted that the usual cordless base stations emit RF-EMF continuously. They are often installed in offices close to the person using a cordless phone handset or in homes even in bedrooms next to the head of a sleeping person.

The real increase in use and exposure to electromagnetic fields from wireless phones (mobile phones and cordless phones) in most countries has occurred since the end of the 1990s. When used they emit RF-EMFs. The GSM phones and to a lesser extent the cordless phones emit also ELF-EMF from the battery when used [4,5]. The brain is the main target organ during use of the handheld phone [6]. Thus, fear of an increased risk for brain tumours 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 impairment of DNA repair mechanisms and epigenetic changes to DNA.

Primary brain tumours (central nervous system; CNS) constitute of a heterogeneous group of neoplasms divided into two major groups; malignant and benign. They are 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 tumour type.

Ionising radiation is an established risk factor for primary brain tumours [7], but there are no well-established environmental causes. Higher socio-economic status tends to be related to higher incidence and some rare inherited cancer syndromes account for a small fraction of tumours [7]. Familial aggregation of glioma has been reported. In a large study 77% more glioma cases than expected were reported among family members [8].

The purpose of this article is to give a comprehensive review of the association between use of mobile and cordless phones and brain tumours, primarily based on the results of the major publications in this field. We include the Hardell group papers and the WHO Interphone study [9–11]. Also some additional analyses of the risk for brain tumours based on these results are given. Some early studies not part of these two major study groups are also included. More discussion of the results and responses, agreements and disagreements of the findings for the Hardell group and Interphone studies can be found elsewhere [12]. In addition, this review includes studies published after the IARC evaluation in May 2011.

## 2. 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 comprehensive a review as possible. All of the authors have long experience in this research area and have published the pioneer studies indicating an association between use of wireless phones and certain types of brain tumours. They represent different supportive areas of competence such as oncology, cancer epidemiology, statistics and physics.

Table 1
Summary of studies on the use of mobile phones and brain tumour risk.

| Study | Years; study type | Age | Tumour type | No. of exposed cases | Odds ratio, 95% confidence interval | Comments |
|---|---|---|---|---|---|---|
| Hardell et al. [15,16] Sweden | 1994–1996; Case-control | 20–80 years | Brain tumours ($n = 209$) | 78 | OR 0.98 (0.69–1.41) | Analogue and digital mobile phone use |
| | | | | 34 | OR 1.07 (0.64–1.80) | *Ipsilateral* mobile phone use |
| | | | | 16 | OR 1.20 (0.56–2.59) | >10 year latency, analogue mobile phone use |
| Muscat et al. [17] USA | 1994–1998; Case-control | 18–80 years | Brain tumours ($n = 469$) | 66 | OR 0.8 (0.6–1.2) | Mean duration of mobile phone use 2.8 years |
| | | | Neuorepithelioma ($n = 35$) | 14 | OR 2.1 (0.9–4.7) | |

### 2.1. Statistical methods

All analyses in the Hardell group studies were done using StataSE 10.1 (Stata/SE 10.1 for Windows; StataCorp., College Station TX). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression analysis. Further details can be found in the publications.

Meta-analyses were performed on use of mobile phones in the Hardell group [13,14] and Interphone group [9,10] studies. No duplicate data from different articles published by the same group of authors were included. Model was chosen based on test for heterogeneity in the overall ($\geq$10 years and $\geq$1640 h) groups. In the analysis of survival of patients with glioma, Cox proportional hazards model was used to calculate hazard ratios (HR) and corresponding 95% confidence intervals. Follow-up time was counted from the date of diagnosis to the date of death or until May 30, 2012 for living cases.

## 3. Results

### 3.1. Brain tumours overall

The first study by Hardell et al. [15,16] included cases and controls during 1994–1996 in parts of Sweden and was the first published study on this issue. Only living cases diagnosed during 1994–1996 were included. Two controls were selected to each case from the Population Registry. In total 209 (90%) of the cases and 425 (91%) of the controls that met the inclusion criteria answered the mailed questionnaire. Overall no association between mobile phone use and brain tumours was found. A slightly increased, but not statistically significant, risk was found for analogue phone (NMT) use and for a latency period greater than 10 years, OR = 1.20, 95% CI = 0.56–2.59, Table 1.

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 [6]. For tumours 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 tumour appeared, yielding OR = 2.42, 95% CI = 0.97–6.05 [16]. This was the first study in the world that indicated an association between use of mobile phones and an increased risk for brain tumours. However, all results were based on low numbers of exposed subjects and different histopathological types of brain tumours so no firm conclusions could be drawn. Furthermore, this first study did not include use of cordless phones.

Muscat et al. [17] studied patients with malignant brain tumours from five different hospitals in USA, Table 1. Controls were hospital patients. Data from 469 (82%) cases and 422 (90%) controls were available. Overall no association was found, OR for handheld cellular phones was 0.8, 95% CI = 0.6–1.2, but the mean duration of use was short, only 2.8 years for cases and 2.7 years for controls. For neuroepithelioma OR = 2.1, 95% CI = 0.9–4.7, was reported. The study was inconclusive since no data were available on long-term users ($\geq$10 years latency period). Some support of an association was obtained since of 41 evaluable tumours, 26 occurred at the side of the head mostly used during calls and 15 on the contralateral side.

### 3.2. Glioma

Glioma is the most common malignant brain tumour and represents about 60% of all central nervous system tumours. The most common glioma subtype is astrocytoma. Astrocytic tumours 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 peak incidence is between 45 and 75 years of age with median survival less than one year [18].

In the study by Hardell et al. [15] analysis of the cases with astrocytoma produced OR = 1.09, 95% CI = 0.64–1.84 ($n = 36$ cases), Table 2. OR increased further for ipsilateral exposure for right sided tumours, OR = 1.30, 95% CI = 0.54–3.13 ($n = 13$ cases), whereas no association was

Table 2
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. [15] Sweden | 1994–1996; Case-control | 20–80 years | Astrocytoma WHO grade I–IV ($n = 94$) | 36 | OR 1.09 (0.64–1.84) | Analogue and digital mobile phone use |
| | | | | 13 | OR 1.30 (0.54–3.13) | *Ipsilateral* mobile phone use, *right* sided tumours |
| | | | | 3 | OR 0.35 (0.07–1.81) | *Ipsilateral* mobile phone use, *left* sided tumours |
| Inskip et al. [19] USA | 1994–1998; Case-control | ≥18 years | Glioma ($n = 489$) | 11 | OR 0.6 (0.3–1.4) | ≥5 years of mobile phone use |
| Auvinen et al. [20] Finland | 1996; Case-control, register based | 20–69 years | Glioma ($n = 198$) | Not given | OR 1.5 (1.0–2.4) | Analogue and digital mobile phone "ever" use |
| | | | | 25 | OR 2.1 (1.3–3.4) | Analogue mobile phone "ever" used |
| | | | | 11 | OR 2.4 (1.2–5.1) | Analogue mobile phone use, 1–2 years |
| | | | | 11 | OR 2.0 (1.0–4.1) | Analogue mobile phone use, >2 years |
| Hardell et al. [26–28] Carlberg, Hardell [29] 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) |
| Interphone Study Group [9] 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 h |
| | | | | 78 | OR 1.87 (1.09–3.22) | Cumulative hours mobile phone ≥1640 h, tumours in *temporal lobe* |
| | | | | 100 | OR 1.96 (1.22–3.16) | Cumulative hours mobile phone ≥1640 h, *ipsilateral* mobile phone use |
| Interphone Study Group [9] Appendix 2 | 2000–2004, 2–4 years depending on study region. Case-control | 30–59 years | 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 h, <5 h as reference entity |

seen for astrocytoma in the left hemisphere and ipsilateral exposure, OR = 0.35, 95% CI = 0.07–1.81 ($n$ = 3 cases).

The study by Inskip et al. [19] from USA had few long-term users of mobile phones. Only 11 cases with glioma, 6 with meningioma and 5 with acoustic neuroma had ≥5 years regular use. No subject had ≥10 years use. Of the hospital-based cases 92% participated. The study comprised 489 cases with glioma, 197 with meningioma and 96 with acoustic neuroma, and 799 (86%) hospital-based controls. Proxy interviews were necessary for 16% of the patients with glioma, 8% of the patients with meningioma, 3% of the patients with acoustic neuroma, and 3% of the controls. Overall no statistically significant associations were found, Table 2. Regarding different types of glioma OR = 1.8, 95% CI = 0.7–5.1 was found for anaplastic astrocytoma (WHO grade III). Regarding hospital-based interviews and use of proxy interviews, see discussion below in relation to the Interphone study.

A register based case-control study on brain and salivary gland tumours was performed in Finland [20]. All cases aged 20–69 years diagnosed in 1996 were included; 398 brain tumour cases and 34 salivary gland tumour cases. The duration of mobile phone use was short, for analogue users 2–3 years and for digital users less than one year. No association was found for salivary gland tumours. For glioma OR = 2.1, 95% CI = 1.3–3.4 was calculated for use of analogue phones, but no association was found for digital mobile phones, Table 2. When duration of use of analogue phones was used as a continuous variable an increased risk was found for glioma with OR = 1.2, 95% CI = 1.1–1.5 per year of use.

The Hardell group in Sweden studied the association between use of mobile and cordless phones and brain tumours diagnosed during 1997–2003. First, cases diagnosed during 1 January 1997 to 30 June 2000 were included. These results were published separately [21,22]. This was followed by the next study period, 1 July 2000 to 31 December 2003 [23,24]. The methods were the same including the same inclusion criteria and an identical questionnaire in both studies; see the publications for further details.

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 with a brain tumour verified by histopathology. The Swedish Population Registry was used for identification of matched controls. The study included use of wireless phones (mobile and cordless phones), as well as asking questions on e.g., occupational 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; >50% of the time for one side, or equally for both sides. This information was checked during the supplementary phone calls and finally also by a separate letter with good agreement between these three methods.

Tumour localisation for the cases was defined by using medical records including computer tomography (CT) and/or magnetic resonance imaging (MRI). The matched control was assigned the same side as the tumour of the respective case. Use of the wireless phone was defined as ipsilateral (≥50% of the time), or contralateral (<50% of the time) in relation to tumour side. Further details can be found in the publications.

In a review commissioned by the former Swedish Radiation Protection Agency (now called the Swedish Radiation Safety Authority) it was suggested that the exclusion of deceased cases was a source of bias in our studies [25]. As a response to that critique we performed a study on the cases with a malignant brain tumour 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 mobile phones and malignant brain tumours [26].

The Hardell group has previously published pooled analysis of malignant brain tumours diagnosed during the period 1997–2003 [27]. These results were updated including also results for deceased cases with malignant brain tumours [28,29]. The results on use of wireless phones were based on 1251 cases with malignant brain tumour (response rate 85%) and 2438 controls (response rate 84%).

Most cases had glioma ($n = 1148$) so we present in the following results for that type of tumour. 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 2. 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 a doubling of glioma risk.

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 [29]. Separate calculations of mobile phone and cordless phone use yielded similar results with statistically significant increasing risks.

It is common for a person to use both a mobile and a cordless phone. For only use of mobile phone OR increased for glioma with time since first use yielding for >10 years latency OR = 2.6, 95% CI = 1.7–4.1. For only cordless phone use highest risk was obtained in the >5–10 years latency time; OR = 1.9, 95% CI = 1.3–2.9. However, the calculations in the longest latency period were based on few subjects regarding cordless phone.

In Table 2 results are presented for high-grade astrocytoma ($n = 820$). The results are similar as for the whole glioma group. Low-grade glioma is less common and the results in this study were based on 132 cases. Ipsilateral use of mobile phone yielded in total OR = 1.8, 95% CI = 1.02–3.1 ($n = 39$ cases) and cordless phone OR = 1.7, 95% CI = 0.98–3.1 ($n = 34$ cases, data not in Table). Further results and discussion may be found elsewhere [29].

The Interphone study was conducted at 16 research centres in 13 countries during varying time periods between 2000 and 2004. It was an international collaboration on brain tumour risk and mobile phone use conducted under the guidance of IARC. The investigation was initiated by recommendations from several expert groups including one of the authors, Kjell Hansson Mild as a member of the EU group, to study possible health effects of exposure to RF-EMF [30,31]. It should be noted that there was no overlap of cases or controls between the Hardell group studies and the Swedish part of Interphone performed by another research group.

Some of the separate country analyses of the Interphone study produced contradictory results, as we have discussed elsewhere [13,32]. An increased risk for brain tumour was found in some studies and decreased risk in other studies. After several years of delay the overall Interphone results were finally published in May 2010 [9].

The study included 4301 glioma cases and the results were based on 2708 participating cases (response rate 64%, range by centre 36–92%). In total 14,354 potential controls were identified and interviews were completed with 7658 (53%, range 42–74%). The low participation rates in some centres may have created selection bias, see Hardell et al. [32].

Regular use of mobile phone in the past ≥1 year gave for glioma OR = 0.81, 95% CI = 0.70–0.94, Table 2. Subgroup analyses showed statistically significant increased risk in the highest exposure group, i.e., those with cumulative mobile phone use ≥1640 h, which corresponds to about half an hour of use per day for ten years, 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 ≥1640 h and ipsilateral exposure produced OR = 1.96, 95% CI = 1.22–3.16 in total (no data given for temporal lobe).

In Appendix 2, available on the web [9] analysis was restricted to ever-regular users of mobile phones in the Interphone study. Cumulative call time ≥1640 h gave OR = 1.82, 95% CI = 1.15–2.89 compared with use <5 h. 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*" [33]. They also pointed out several methodological reasons why the Interphone results were likely to have underestimated the risks, such as 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*".

As has pointed our elsewhere [32] there were differences between the Hardell group studies and Interphone. Regarding age group the Hardell group studies included subjects aged 20–80 years, versus 30–59 years in Interphone. Furthermore use of cordless phones was not properly assessed, analysed or reported in Interphone. These differences have been discussed in detail by Hardell et al. [14]. Thus, it could be 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 OR and produced results quite similar to Interphone, Table 3; see also Table 11 as discussed below. 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 ≥10 years). Unfortunately the Interphone study did not give results for glioma in the temporal lobe in the analyses in Appendix 2. 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, which likely dilutes the ability to see health risks.

Most mobile phone users have not been using one single telephone. It is likely that they have changed their handset several times if they have been using a mobile phone for more than a few years. Many users have also been using different phone systems, such as analogue and digital, and many of them have also been using a cordless phone at home or at work. It is not clear how to combine the use of different phones with different power outputs, systems, frequencies and anatomical specific absorption rate (SAR) distributions into one exposure and dose measure. The difficulties lie in the fact that there is no generally accepted mechanism(s) between the electromagnetic fields emitted from the phone and the biological organism. This includes a mechanism by which RF-EMF exposure produces changes in DNA. The energy level associated with exposure is too low to cause direct DNA strand breaks and DNA cross links. However, DNA damages can be caused by cellular biochemical activities such as free radicals. Several studies indicate that RF-EMFs increase free radical activity in cells, as reviewed by Phillips et al. [34]. This process is probably mediated via the Fenton reaction. It should also be noted that possible biological effects might not have linear dose–response as indicated in some studies [35] and that the effects are depending on the carrier frequencies [36].

The different types of phones have different output power. We applied different weighting factors according to the mean output power of the phones using for analogue phones (NMT) = 1, GSM = 0.1 and cordless phones = 0.01. The cumulative time for use of the different phone types was multiplied with the respective weighting factor added into one score. The median score among the controls was used as the cut-off in the dose–response calculations. We applied this method for the study period 1 January 1997 to 30 June 2000 [21,22]. Somewhat higher ORs were obtained using the weighting factor, especially with a >10-year latency period, compared with calculations based on cumulative use only, but overall the results were similar [37]. This was explained by the fact that most subjects had used an analogue mobile phone with the weighting factor = 1, thus the weighting factor had little impact on the results.

A further issue is that there is a difference in the output power level from mobile phones between urban and rural areas. This is caused by adaptive power control (APC) in the cellular telephone and is regulated by the distance between base stations. Thus, in areas with a long distance between base stations, usually rural areas, the output power level is higher than in more densely populated areas; that is, urban areas, with a shorter distance between base stations. To further explore these circumstances we used the Swedish population register that contains information on present municipality for all residents. The municipalities are classified by Statistics Sweden into so called homogeneity regions, six categories depending on the population density, and the number of inhabitants in the nearest vicinity of the main city in that municipality. Thus, we used these official statistics for grouping of the subjects in urban or rural areas for the study period 1 January 1997 to 30 June 2000. For use of digital mobile phones (GSM) we found a clear effect of urban versus rural areas [38]. Living in rural areas yielded OR = 1.4, 95% CI = 0.98–2.0, increasing to 3.2, 95% CI = 1.2–8.4 with >5 year latency time for digital phones. The corresponding ORs for living in urban areas were 0.9, 95% CI = 0.8–1.2 and 0.9, 95% CI = 0.6–1.4, respectively. This effect was most obvious for malignant brain tumours.

Estimated RF-EMF dose from mobile phone use in the tumour area was associated with an increased risk of glioma in parts of the Interphone study [11]. OR increased with increasing total cumulative dose of specific energy (J/kg) absorbed at the estimated tumour 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 sound methods was later published by another part of the Interphone study group [39]. The results seemed to contradict the findings of Cardis et al. [11]. However, a different, less clear method was used. Only 42 cases had used mobile phone for more than 10 years and no analysis was made of the most exposed group with longest duration of use. Thus, this study is much less informative and less sophisticated than the one by Cardis et al. [11]. It should have been of great value to apply the method by Cardis et al. for the whole Interphone study.

Table 3
Comparison between Hardell group and Interphone using the same age group 30–59 years and excluding use of cordless phones.

| Study | Years; study type | Age | Tumour type | No. of exposed cases | Odds ratio, 95% confidence interval | Comments |
|---|---|---|---|---|---|---|
| Hardell et al. [14] | 1997–2003; Case-control | 30–59 years | Glioma ($n = 490$) | 56 | OR 1.79 (1.19–2.70) | >10 year latency, cordless phone among unexposed, age 30–59 years |
| | | | | 29 | OR 1.75 (1.02–3.00) | Cumulative use ≥1640 h, cordless phone among unexposed, age 30–59 years |
| | | | | 20 | OR 2.18 (1.09–4.35) | Cumulative use ≥1640 h, cordless phone among unexposed, age 30–59 years, *ipsilateral* |
| | | | | 8 | OR 1.48 (0.57–3.87) | Cumulative use ≥1640 h, cordless phone among unexposed, age 30–59 years, *contralateral* |
| Interphone Study Group [9] 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 ($n = 2708$) | 252 | OR 0.98 (0.76–1.26) | Regular use of mobile phone in the past ≥1 year, latency ≥10 years |
| | | | | 210 | OR 1.40 (1.03–1.89) | Cumulative hours mobile phone ≥1640 h |
| | | | | 100 | OR 1.96 (1.22–3.16) | Cumulative hours mobile phone ≥1640 h, *ipsilateral* |
| | | | | 39 | OR 1.25 (0.64–2.42) | Cumulative hours mobile phone ≥1640 h, *contralateral* |
| | | | | 160 | OR 1.82 (1.15–2.89) | Restricted to *ever regular use* ≥1640 h, <5 h as reference entity, Appendix 2. Results for ipsilateral and contralateral use not reported. |

Table 4
Use of mobile phones and glioma risk, meta-analysis of Hardell et al. [14] and Interphone [9]. Numbers of exposed cases (Ca) and controls (Co) are given.

| | Hardell et al. | | Interphone | | Meta-analysis | |
|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Latency ≥10 years* | | | | | | |
| -all | 88/99 | 2.26 (1.60–3.19) | 252/232 | 0.98 (0.76–1.26) | 340/331 | 1.48 (0.65–3.35) |
| -ipsilateral | 57/45 | 2.84 (1.82–4.44) | 108/82 | 1.21 (0.82–1.80) | 165/127 | 1.84 (0.80–4.25) |
| -contralateral | 29/29 | 2.18 (1.24–3.85) | 49/56 | 0.70 (0.42–1.15) | 78/85 | 1.23 (0.40–3.73) |
| -temporal lobe | 28/99 | 2.26 (1.32–3.86) | 94/69 | 1.36 (0.88–2.11) | 122/168 | 1.71 (1.04–2.81) |
| *Cumulative use ≥1640 h* | | | | | | |
| -all | 42/43 | 2.31 (1.44–3.70) | 210/154 | 1.40 (1.03–1.89) | 252/197 | 1.74 (1.07–2.83) |
| -ipsilateral | 29/21 | 2.94 (1.60–5.41) | 100/62 | 1.96 (1.22–3.16) | 129/83 | 2.29 (1.56–3.37) |
| -contralateral | 12/12 | 2.10 (0.90–4.90) | 39/31 | 1.25 (0.64–2.42) | 51/43 | 1.52 (0.90–2.57) |
| -temporal lobe | 14/43 | 2.44 (1.21–4.95) | 78/47 | 1.87 (1.09–3.22) | 92/90 | 2.06 (1.34–3.17) |

Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1640 h) groups.

### 3.3. Meta-analysis glioma

We performed a meta-analysis of glioma on use of mobile phones based on Hardell et al. [14] and Interphone Study Group [9]. Random-effects model was used based on test for heterogeneity in the overall (≥10 years and ≥1640 h) groups. The analysis was based on published results in Interphone since we do not have access to their database. Our results were recalculated to these groups of exposure. Thus, results can be found in Table 4 for latency ≥10 years, (>10 years in Hardell et al.), and cumulative use of mobile phone ≥1640 h. 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 ≥1640 h in total gave the highest risk, OR = 2.29, 95% CI = 1.56–3.37. Certainly the meta-analysis strengthens a causal association between use of mobile phones and glioma.

### 3.4. Meningioma

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

In the first study by Hardell et al. [15] only 46 cases had meningioma. No increased risk was found overall; OR = 1.05, 95% CI = 0.49–2.27, Table 5. Only 16 cases had used a mobile phone. There was no pattern of increased risk for ipsilateral use, although the results were based on low numbers.

The US study by Inskip et al. [19] included 197 cases with meningioma. Regular mobile phone use produced OR = 0.8, 95% CI = 0.4–1.3, Table 5. The risk did not increase with average daily use, cumulative use, or duration of regular use. However, results for duration of regular use ≥5 years was based on only 6 exposed cases.

The Finnish register based case-control study on brain tumours by Auvinen et al. [20] included 129 cases with meningioma. Ever use of mobile phone gave OR = 1.1, 95% CI = 0.5–2.4, analogue phone use OR = 1.5, 95% CI = 0.6–3.5, Table 5. As discussed above the study was limited by short latency and exposure based on subscription information.

The Hardell group made a pooled analysis of benign brain tumours from the two case-control studies 1997–2003 as discussed above [40,41]. Regarding meningioma use of mobile phone gave OR = 1.1, 95% CI = 0.9–1.3, and cordless phone OR = 1.1, 95% CI = 0.9–1.4, Table 5. 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.

In the Interphone study [9] a statistically significant decreased risk was found for meningioma for regular use of mobile phone, OR = 0.79, 95% CI = 0.68–0.91, Table 5. The risk increased somewhat with cumulative use ≥1640 h and ipsilateral mobile phone use to OR = 1.45, 95% CI = 0.80–2.61. The overall pattern of no association did not change if analysis was restricted to tumours in the temporal lobe or only to the group of ever-regular use.

### 3.5. Meta-analysis meningioma

Similarly as for glioma we performed meta-analysis of meningioma for use of mobile phone on the Hardell group and Interphone results, Table 6. Random-effects model was used in the ≥10 years group based on test for heterogeneity in the overall group. For analyses of ≥1640 h no heterogeneity was found in the heterogeneity test; random- and fixed effects models produced identical results. In summary no statistically significant decreased or increased risks were found. These results support the conclusion that up to latency ≥10 years or cumulative use ≥1640 h there is not a consistent pattern of an association between use of mobile phones and meningioma.

Table 5
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. [15] Sweden | 1994–1996; Case-control | 20–80 years | Meningioma ($n = 46$) | 16 | OR 1.05 (0.49–2.27) | Analogue and digital mobile phone use |
| Inskip et al. [19] USA | 1994–1998; Case-control | ≥18 years | Meningioma ($n = 197$) | 32 | OR 0.8 (0.4–1.3) | Regular use |
| | | | | 6 | OR 0.9 (0.3–2.7) | ≥5 years of mobile phone use |
| Auvinen et al. [20] Finland | 1996; Case-control, register based | 20–69 years | Meningioma ($n = 129$) | Not given | OR 1.1 (0.5–2.4) | Analogue and digital mobile phone "ever" use |
| | | | | 8 | OR 1.5 (0.6–3.5) | Analogue mobile phone "ever" used |
| | | | | 3 | OR 1.6 (0.4–6.1) | Analogue mobile phone use, 1–2 years |
| | | | | 2 | OR 1.0 (0.2–4.4) | Analogue mobile phone use, >2 years |
| Hardell et al. [40], Hardell, Carlberg [41] 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 use |
| | | | | 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 [9] 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 h |
| | | | | 21 | OR 0.94 (0.31–2.86) | Cumulative hours mobile phone ≥1640 h, tumours in *temporal lobe* |
| | | | | 46 | OR 1.45 (0.80–2.61) | Cumulative hours mobile phone ≥1640 h, *ipsilateral* mobile phone use |
| Interphone [9] Appendix 2 | | | 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 h, <5 h as reference entity |

Table 6
Use of mobile phones and meningioma risk, meta-analysis of Hardell, Carlberg [41] and Interphone [9]. Numbers of exposed cases (Ca) and controls (Co) are given.

| | Hardell et al. | | Interphone | | Meta-analysis | |
|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Latency ≥10 years* | | | | | | |
| -all | 38/99 | 1.52 (0.98–2.37) | 110/112 | 0.83 (0.61–1.14) | 148/211 | 1.10 (0.61–1.99) |
| -ipsilateral | 18/45 | 1.59 (0.86–2.95) | 40/42 | 0.88 (0.52–1.47) | 58/87 | 1.16 (0.65–2.06) |
| -contralateral | 12/29 | 1.57 (0.75–3.31) | 20/25 | 0.58 (0.29–1.16) | 32/54 | 0.95 (0.36–2.51) |
| -temporal lobe | 10/99 | 2.46 (1.08–5.60) | 12/12 | 0.60 (0.22–1.62) | 22/111 | 1.25 (0.31–4.98) |
| *Cumulative use ≥1640 h* | | | | | | |
| -all | 10/43 | 0.85 (0.41–1.75) | 130/107 | 1.15 (0.81–1.62) | 140/150 | 1.09 (0.80–1.49) |
| -ipsilateral | 6/21 | 1.11 (0.42–2.88) | 46/35 | 1.45 (0.80–2.61) | 52/56 | 1.35 (0.81–2.23) |
| -contralateral | 3/12 | 0.98 (0.26–3.61) | 28/28 | 0.62 (0.31–1.25) | 31/40 | 0.69 (0.37–1.27) |
| -temporal lobe | 1/43 | 0.52 (0.07–3.95) | 21/14 | 0.94 (0.31–2.86) | 22/57 | 0.82 (0.31–2.17) |

Random-effects model used for meta-analyses of ≥10 years, based on test for heterogeneity in the overall group. For meta-analyses of ≥1640 h no heterogeneity was found; random- and fixed effects models produced identical results.

### 3.6. Acoustic neuroma

Acoustic neuroma or Vestibular Schwannoma is a benign tumour that is located in the eighth cranial nerve that leads from the inner ear to the brain. This tumour type does not undergo malignant transformation. It tends to be encapsulated and grows in relation to the auditory and vestibular portions of the nerve. It is a slow growing tumour in the auditory canal but 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. Although neuroma is a benign tumour it causes persistent disabling symptoms after treatment such as loss of hearing and tinnitus that severely affect the daily life. 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 RF-EMF emissions during use of these devices.

In the first study by Hardell et al. [15] in Sweden only 13 cases had acoustic neuroma. Five cases reported use of mobile phone, only one with ipsilateral use. The numbers were too low to make meaningful interpretation of an association, Table 7.

Inskip et al. [19] included 96 cases with acoustic neuroma in their US case-control study. No increased risk was found for regular use of mobile phone, Table 7. Duration of regular use ≥5 years gave OR = 1.9, 95% CI = 0.6–5.9. This result was based on only 5 exposed cases and there were no results on long-term use. Furthermore only 1 case had cumulative use >500 h.

Muscat et al. [42] presented results from a hospital based case-control study on acoustic neuroma on 90 (100% response rate) patients and 86 (100%) controls. Mobile phone use 1–2 years gave OR = 0.5, 95% CI = 0.2–1.3 ($n = 7$ cases), increasing to OR = 1.7, 95% CI = 0.5–5.1 ($n = 11$ cases), in the group with 3–6 years use, Table 7. Average use among cases was 4.1 years and among controls 2.2 years.

The pooled analysis of the Hardell group studies yielded in total OR = 2.9, 95% CI = 2.0–4.3 for use of analogue mobile phone and OR = 1.5, 95% CI 1.1–2.1 for use of digital mobile phone [40]. Use of mobile phones gave 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 7. Ipsilateral use increased the risk further; in the >10 years latency group to OR = 3.0, 95% CI = 1.4–4.2 [41]. 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.

A case-case study on acoustic neuroma was conducted in Japan [43]. The cases were identified during 2000–2006 at 22 participating neurosurgery departments. The diagnosis was based on histopathology or CT/MRI imaging. Of 1589 cases 816 (51%) agreed to participate and answered a mailed questionnaire. A total of 787 cases were included in the final analysis. Two datasets were analysed, one consisted of 362 cases without any tumour related symptoms 1 year before diagnosis, and another consisted of 593 cases without any symptoms 5 years before diagnosis. 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 min with reference date 1 year Risk Ratio (RR) = 2.74, 95% CI = 1.18–7.85 was found increasing to RR = 3.08, 95% CI = 1.47–7.41 with reference date 5 years before diagnosis, Table 7. 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.

In the Interphone study [10] 1121 (82%) acoustic neuroma cases participated, range 70–100% by centre. Of the controls 7658 (53%) completed the interviews, range 35–74% by centre. The final matched analysis (1:1 or 1:2) consisted of 1105 cases and 2145 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 7.

Cumulative number of hours of ipsilateral mobile phone use ≥1640 h up to 1 year before reference date gave OR = 2.33, 95% CI = 1.23–4.40 and contralateral use

Table 7
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. [15] Sweden | 1994–1996; Case-control | 20–80 years | Acoustic neuroma ($n = 13$) | 5 | OR 0.78 (0.14–4.20) | >1 year latency of mobile phone use |
| Inskip et al. [19] USA | 1994–1998; Case-control | ≥18 years | Acoustic neuroma ($n = 96$) | 22 | OR 1.0 (0.5–1.9) | Regular mobile phone use |
| | | | | 5 | OR 1.9 (0.6–5.9) | ≥5 years of mobile phone use |
| Muscat et al. [42] USA | 1997–1999; Case-control | ≥18 years | Acoustic neuroma ($n = 90$) | 11 | OR 1.7 (0.5–5.1) | 3–6 years of mobile phone use |
| Hardell et al. [40], Hardell, Carlberg [41] 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. [43] 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 |
| Interphone Study Group [10] 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 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Interphone [10] 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 ($n = 1105$) | 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 h up to 1 year before reference date |
| | | | | 36 | OR 2.79 (1.51–5.16) | Cumulative hours mobile phone ≥1640 h up to 5 years before reference date |
| | | | | 47 | OR 2.33 (1.23–4.40) | Cumulative hours mobile phone ≥1640 h up to 1 year before reference date; *ipsilateral* use |
| | | | | 27 | OR 3.53 (1.59–7.82) | Cumulative hours mobile phone ≥1640 h up to 5 years before reference date; *ipsilateral* use |
| | | | | 37 | OR 1.93 (1.10–3.38) | Cumulative hours mobile phone ≥1640 h in the past start ≥10 years before reference date |
| | | | | 28 | OR 3.74 (1.58–8.83) | Cumulative hours mobile phone ≥1640 h 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 h, <5 h as reference entity |

OR = 0.72, 95% CI = 0.34–1.53 for acoustic neuroma, Table 7 [10]. For cumulative number of hours of ipsilateral mobile phone use ≥1640 h 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 ≥1640 h with start ≥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 ≥10 years before reference date and cumulative call time ≥1640 h.

Similar analyses of the data as in Appendix 2 for glioma [9], 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 [10]. 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 ≥1640 h; OR = 1.74, 95% CI = 0.90–3.36, in this analysis restricted to only regular users. No results were given for ipsilateral use.

### 3.7. Meta-analysis acoustic neuroma

Table 8 shows results for use of mobile phone and the association with acoustic neuroma based on results by the Hardell group and Interphone study. Random-effects model was used based on test for heterogeneity in the overall (≥10 years and ≥1640 h) groups. The same exposure groups as in the meta-analyses of glioma and meningioma were used. 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 ≥1640 h 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.

### 3.8. Other types of brain tumours

Results for other types of brain tumours from the Hardell group diagnosed during 1997–2003 included medulloblastoma ($n = 6$), ependymoma ($n = 19$) and other malignant types ($n = 46$). In total using >1 year latency time no statistically significant increased risk was found for mobile phone use, OR = 1.2, 95% CI = 0.7–2.1 for these tumour types grouped together [41]. However, with >10 years latency the risk increased to OR = 3.2, 95% CI = 1.2–8.8 in total; for ipsilateral use OR = 4.1, 95% CI = 1.03–16. For cordless phone use no statistically significant decreased or increased risk was found (data not in Table). For pituitary adenoma ($n = 34$) and other types of benign brain tumours ($n = 62$) no statistically significant associations were found overall. In the >10 year latency group ipsilateral mobile phone use gave OR = 4.7, 95% CI = 1.1–21 for benign tumours other than pituitary adenoma (central location in the brain and not included in these calculations) but based on only 4 exposed cases. Thus, several of the calculations were based on low numbers.

Takebayashi et al. [44] included 102 cases with pituitary adenoma in the Japanese part of Interphone from December 2000 to November 2004. The response rate was 76%; 102 out of 135 cases. Of the individually matched controls 208 (49%) of 421 participated. In the statistical analysis 161 controls were used to 101 cases; one case was excluded since not diagnosed within study period. Regular mobile phone use yielded OR = 0.90, 95% CI = 0.50–1.61. Cumulative length of use in years or cumulative call time in hours produced no pattern of an association and there was no statistically significant trend. The cut off for highest quartile of cumulative use was 560 h producing OR = 1.33, 95% CI = 0.58–3.09 ($n = 21$ cases, 27 controls exposed). Since pituitary adenoma is a centrally located tumour in the pituitary gland in sella turcica there was no laterality analysis.

In parallel with the Interphone study, pituitary tumours were studied in Southeast England using the same protocol [45]. The inclusion period was from December 2000 until February 2005. In total 506 eligible cases were identified. Of them 317 (63%) were interviewed and 291 (58%) included in the final analysis. Eligible controls from patient lists at general practitioners in the study region were 1464 subjects, and 630 (43%) were interviewed. Regular use of mobile phone gave OR = 0.9, 95% CI = 0.7–1.3. No statistically significant trend for the risk was found for lifetime use in years or cumulative use in hours. For ≥10 years since first use and ≥51 h of cumulative use (median number in that category) OR = 1.6, 95% CI = 0.8–3.6 ($n = 16$ cases, 23 controls exposed) was found.

### 3.9. Risks to children and adolescents

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 [6,46,47]. The developing brain is more sensitive to toxins [48] and it is still developing until about 20 years of age [49]. Use of wireless phones is widespread among children and adolescents [50,51]. 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 tumour leaves children at a higher risk than adults from mobile phone radiation.

The Hardell group has published results for different age groups at the time of diagnosis [52] or age at first use of wireless phones [12,13,28]. 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 9. Thus, mobile phone yielded for glioma OR = 3.1, 95% CI = 1.4–6.7 and cordless phone OR 2.6, 95% CI = 1.2–5.5. The risk increased further for ipsilateral mobile phone use in the youngest age group to OR = 4.4,

Table 8
Use of mobile phones and acoustic neuroma risk, meta-analysis of Hardell, Carlberg [41] and Interphone [10]. Numbers of exposed cases (Ca) and controls (Co) are given.

| | Hardell et al. | | Interphone | | Meta-analysis | |
|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Latency ≥10 years* | | | | | | |
| -all | 20/99 | 2.93 (1.57–5.46) | 68/141 | 0.76 (0.52–1.11) | 88/240 | 1.46 (0.39–5.47) |
| -ipsilateral | 13/45 | 2.97 (1.42–6.21) | 44/52 | 1.18 (0.69–2.04) | 57/97 | 1.81 (0.73–4.45) |
| -contralateral | 6/29 | 2.38 (0.89–6.35) | 17/30 | 0.69 (0.33–1.42) | 23/59 | 1.22 (0.37–4.11) |
| *Cumulative use ≥1640 h* | | | | | | |
| -all | 10/43 | 2.86 (1.33–6.14) | 77/107 | 1.32 (0.88–1.97) | 87/150 | 1.81 (0.86–3.81) |
| -ipsilateral | 7/21 | 3.10 (1.21–7.95) | 47/46 | 2.33 (1.23–4.40) | 54/67 | 2.55 (1.50–4.40) |
| -contralateral | 3/12 | 2.28 (0.60–8.71) | 16/26 | 0.72 (0.34–1.53) | 19/38 | 1.12 (0.37–3.34) |

Random-effects model used for all meta-analyses, based on test for heterogeneity in the overall (≥10 years and ≥1640 h) groups.

95% CI = 1.3–15 for mobile phone use and to OR = 4.3, 95% CI = 1.4–13 for cordless phone use.

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 increasing to OR = 6.8, 95% CI = 1.4–34 for ipsilateral use. 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.

There are few other studies on brain tumour risk for children from use of wireless phones. Mobikids is one study that is on-going. A multi-centre case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO [53]. 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 [54].

In CEFALO a statistically non-significant increased risk for brain tumours 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 [53]. No data for long-term use were given; the longest latency period was 5 years. Interestingly, 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 not well assessed. The authors stated that such use 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 [1]. Instead Aydin et al. [53] included use of cordless phones in the 'unexposed' category when risk estimates were calculated for mobile phone use. Similarly, when use of cordless phones was analysed mobile phone use was 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 in children and adolescents*." An editorial in the same journal accompanied that conclusion by stating

Table 9
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 [26–28,40]. 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 |
| Wireless phone (mobile and cordless phone) | 670/1267 | 1.3 (1.1–1.5) | 461/1172 | 1.0 (0.9–1.2) | 155/1172 | 1.5 (1.1–2.0) |
| <20 years old | 25/27 | 2.3 (1.3–4.3) | 6/27 | 1.0 (0.4–2.6) | 5/27 | 2.4 (0.8–7.3) |
| 20–49 years old | 377/746 | 1.3 (1.1–1.6) | 276/711 | 1.3 (1.02–1.6) | 103/711 | 1.8 (1.2–2.6) |
| ≥50 years old | 268/494 | 1.3 (1.1–1.6) | 179/434 | 0.9 (0.7–1.2) | 47/434 | 1.3 (0.9–1.9) |
| 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) |

that the study showed "*no increased risk of brain tumors in children and adolescents who are regular cell phone users*" [55]. This was echoed by a news release from the Karolinska Institute in Stockholm claiming that the results of no increased risk were 'reassuring' (http://ki.se/ki/jsp/polopoly.jsp?d=130&a=125250&l=en&newsdep=130). However, these statements go far beyond what the study really showed. In fact, the results indicate a moderately increased risk, in spite of low exposure, short latency period and limitations in study design and analyses. Aydin et al. discussed recall bias – that people tend to overestimate their number of calls – and interestingly they showed that controls overestimated their number of calls more than cases [56]. It was concluded that it was unlikely that a false positive result occurred in CEFALO and that the OR was underestimated for heavy users. Certainly the results in the article [53] cannot be used as reassuring evidence against an association, as discussed in our commentary [54].

### *3.10. Danish cohort study on mobile phone users*

Ideally a cohort study on wireless phone users would be of substantial value. However, several problems exist to establish a cohort with high quality assessed exposure. For example use of both mobile phones and cordless phones vary over time and exposure to RF-EMF emissions also depends on several physical characteristics for different phone types. 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 Sonofon), IEI, and the Danish Cancer Society. The source of money for IEI has not been disclosed.

The first results from the Danish study on brain tumour risk among mobile phone subscribers were published in 2001 [57]. 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. They were expected to be the heaviest users and such exclusion would underestimate any risk estimates. It should be noted that duration of subscription of a digital phone was at most ≥3 years ($n = 9$) and that two thirds of the subscriptions began in 1994 and 1995. In other words, the majority of the cohort members had two years or less of subscription time. This and other shortcomings in this cohort study have been discussed elsewhere in detail [58]. The Danish study was part of the IARC evaluation but it was concluded that the methods used could have resulted in considerable misclassification in exposure assessment [1].

The first update of the Danish study gave follow-up data until 2002 [59]. The median time since first subscription was this time 8.0 years. It was now stated that the cohort members were excluded from the reference population, which seems not to have been the case in the first publication. The Standardised Incidence Ratio (SIR) for glioma was close to unity, SIR = 1.01, 95% CI = 0.89–1.14. The highest SIR was found for glioma in the temporal lobe where RF-EMF exposure from a mobile phone would be highest, SIR = 1.21, 95% CI = 0.91–1.58 ($n = 54$ cases).

After the outcome of the IARC-evaluation was made public in June 2011 [1] two additional reports on the Danish cohort were soon published. Both were new up-dates of mobile phone subscribers and included more information on risk related to longer follow-up. One focused on acoustic neuroma [60] while the other gave results both for all cancers and separately for glioma and meningioma [61].

Approximately 2.9 million of the Danish population of 5.5 million in total was included in the record linkage study on acoustic neuroma [60]. Of the 2.9 million subjects 420,095 were mobile phone subscribers that started their subscription 1987–1995 and in accordance with the aim of the study had lasted for ≥11 years, i.e., 1998–2006 during which period the tumour cases were ascertained. No evidence of an increased risk was found for ≥11 years of subscription; adjusted Incidence Rate Ratio (IRR) was 0.87, 95% CI = 0.52–1.46.

The analysis of long-term exposure (≥11 years) was based on only 15 exposed cases with acoustic neuroma all of which were men. Analysis of tumour size was based on even fewer cases; 8 had a subscription for ≥11 years. As for the risk related to laterality Schüz et al. [60] compared the location of acoustic neuroma in long-term mobile phone subscribers with shorter use (<11 years) and non-subscribers to see if tumours occurred more frequently on the side which was assumed to be the mostly exposed. This assumption was based on ecological data from the prospective study, COSMOS, as proxy for laterality [62]. Due to these facts the argument of no laterality risk is not very impressive, especially when applied to only 15 exposed cases.

The fourth report on the Danish mobile phone cohort on tumours of the central nervous system showed no overall increased risk [61]. This was true also when restricted to the individuals with the longest mobile phone use, ≥13 years of assumed subscription.

This time the number of the cohort was reduced to 358,403 (49.5%) of the initially identified subscribers ($n = 723,421$). This number was also used in the study on acoustic neuroma [60]. The major additional exclusion ($n = 54,350$) was due to record linkage with the Danish so-called CANULI cohort on socioeconomic factors [63]. That register started 1990 and included subjects from the age of 30. Subscription holders aged 18–29 years were excluded from the mobile phone cohort; this was also the case for the third publication (acoustic neuroma), see above. Follow-up of cancer started at January 1, 1990, or at the age of 30 if occurred later, and ended December 31, 2007.

The study period was 1990–2007 [61] but the cohort was established during 1982–1995. Cancer cases before 1990 were disregarded since the CANULI cohort started in 1990.

The authors did not discuss the impact of the exclusion of these subscribers on the results. This exclusion would include the early users of analogue phones, which seem to have had higher emissions of RF-EMF than the later digital system. The authors themselves also stated the following in their discussion: "*. . .we found indications that early subscription holders before 1995 were in fact heavier users (based on outgoing calls) compared with all subscription holders in the years 1996–2002*." Analysis of any early effect in the group who used phones with the highest emissions was most likely hampered. Moreover, also the youngest users, aged 18–29 years that had previously been included, were now excluded from the cohort. The fully adjusted model had no substantial effect on the risk estimates, so results adjusted for age and calendar period should be possible also for the youngest users. The exclusion of young subscribers could be of importance since as discussed above studies have indicated highest risk in subjects that started the use of a mobile or cordless phone before the age of 20 [28,41].

Some of the many shortcomings of the Danish cohort study include: (a) no individual exposure data (e.g. on cumulative exposure, side of head mostly used, and use of cordless phones); including users of cordless phones in the reference category; (b) no control for use of mobile phones in the population after the establishment of the cohort; and (c) no operator-verified data on years of subscription was available. These limitations are likely to have led to an underestimate of any risk in this study. One would 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 publication of the latest update of the Danish study [61] was accompanied by an editorial by Ahlbom and Feychting from the Karolinska Institute in Sweden [64]. It began with the statement: "*Evidence is reassuring, but continued monitoring of health registers and prospective cohorts is still warranted*." They pointed out methodological advantages, such as elimination of non-response and selection bias, but did forget to mention that less than 50% of the initial cohort remained for analysis. However, they were more lenient on the methodological limitations that they had previously pointed out as serious. In a letter to the Editor in 2007 on an earlier publication of the same cohort [59] they pointed out that several methodological shortcomings undermined the authors' conclusion that "*any large association of risk of cancer and cellular telephone use can be excluded*" [65]. Although more long-term data was now available and adjustment for socioeconomic factors could be made, the update by Frei et al. [61] suffers from basically the same methodological limitations – mainly related to exposure assessment – as the first one did. Instead of addressing the limitations of the Danish cohort study in full, Ahlbom and Feychting [64] used their space to selectively report on results in the Hardell group studies choosing the time period 2000–2003 [23,24] although the whole investigation period was 1997–2003 [27,40]. They discussed incidence data on brain tumours in Sweden instead of Denmark, which would have been more appropriate regarding a Danish cohort study.

The authors of the Danish study have themselves pointed out the main causes of such considerable exposure misclassifications [61]: mobile phone subscription holders not using the phone were classified as 'exposed', non-subscribers using the mobile phone were classified as 'unexposed'; corporate subscribers of mobile phones (200,507 people), which are likely to have been heavy users, were classified as 'unexposed'; persons with a mobile phone subscription later than 1995 were classified as 'unexposed' and users of cordless phones not using a mobile phone were also classified as 'unexposed'.

Other limitations are the absence of analysis by laterality (the side of head where the phone is used in relation to the side of the tumour) and the complete absence of actual exposure data. These and other shortcomings in the cohort study have been discussed elsewhere in more detail [58,65].

It is clear from these limitations that the authors' conclusion that: "*In this update of a large nationwide cohort study of mobile phone use, there were no increased risks of tumours of the central nervous system, providing little evidence for a causal association*" is not soundly based [61].

### *3.11. Hazard ratio (HR) for survival of patients with glioma*

A poorer survival among children with acute lymphoblastic leukaemia exposed to ELF-EMF has been reported in two studies [66,67]. These findings certainly strengthen a causal association between exposure to ELF-EMF and childhood leukaemia. Thus, a carcinogenic effect of RF-EMF emissions would be strengthened if exposure might correlate with survival of glioma patients. To further elucidate that possibility we analysed survival of all cases with malignant brain tumour ($n = 1251$) in our case-control studies [26–28]. Most cases were diagnosed with glioma ($n = 1132$ in this study) so in the following results for glioma are presented in short, for further details see Hardell and Carlberg [68].

Hazard ratio (HR) for survival was close to unity for all glioma cases for use of wireless phones, HR = 1.1, 95% CI = 0.9–1.2. However, latency >10 years increased HR to 1.2, 95% CI = 1.002–1.5. Increased ratio was found for both mobile phone use, HR = 1.3, 95% CI = 1.0005–1.6, and cordless phone use, HR = 1.3, 95% CI = 0.9–1.9. HR increased also with cumulative number of hours of use of mobile phone and cordless phone with statistically significant trend for tertiles ($p = 0.01$) of use of both phone types.

Regarding different types of astrocytoma wireless phone use gave a decreased HR = 0.5, 95% CI = 0.3–0.9 for low-grade astrocytoma, WHO grades I–II. Similar results were found for both mobile and cordless phones. Latency did not change these results. Also cumulative numbers of hours for use yielded decreased HR for both mobile and cordless phone use.

For anaplastic astrocytoma, WHO grade III, there was no clear pattern of an association for latency or cumulative number of hours for use. On the contrary, for glioblastoma multiforme, WHO grade IV, long-term use >10 years latency of mobile phone increased the ratio, HR = 1.3, 95% CI = 0.9–1.7, and cordless phone, HR = 1.8, 95% CI = 1.2–2.8.

This study showed elevated HR, indicating decreased survival of all glioma cases with long-term and high cumulative use of wireless phones. For astrocytoma WHO grade IV an increased HR was found indicating a survival disadvantage. On the other hand HR was decreased for low-grade astrocytoma, WHO grades I–II, indicating a survival benefit in that group of cases. This could be caused by RF-EMF exposure leading to tumour-associated symptoms and earlier detection and surgery with better prognosis in that patient group [69].

### 3.12. Brain tumour incidence

It has been suggested that overall incidence data on brain tumours for countries may be used to qualify or disqualify the association between mobile phones and brain tumours observed in the case-control studies [53,64,70,71]. As mentioned above, in support of the cohort findings that Frei et al. [61] presented for Denmark, Ahlbom and Feychting [64] refer to data on overall brain tumour incidence from the Swedish Cancer Registry rather than from the Danish Cancer Registry, which would have been more relevant.

In Denmark a statistically significant increase in incidence rate per year for brain and central nervous system tumours (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% (http://www-dep.iarc.fr/NORDCAN/english/frame.asp). Updated results for brain and central nervous system tumours have been released in Denmark. The age-standardised incidence of brain and central nervous system tumours increased with 40% among men and 29% among women during 2001–2010 (http://www.sst.dk/publ/Publ2011/DAF/Cancer/Cancerregisteret2010.pdf). 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). So far these incidence data are not generally available.

Also in the CEFALO study including Denmark, Sweden, Norway and Switzerland [53] only data from the Swedish Cancer Registry were used on time trends for brain tumour incidence. As we have displayed elsewhere [54] annual change in incidence in the age group 5–19 years differs between the Nordic countries. Thus, for the time period 1990–2008 in Norway a yearly increase in incidence with +3.3%, 95% CI +0.8 to 5.9% in boys and +2.5%, 95% CI +0.2 to 4.9% in girls was seen, whereas in Sweden there was a decline in boys and slight increase in girls. Thus, it would have been more appropriate in CEFALO to discuss trends in all included countries.

The quality of the Swedish Cancer Registry for reporting central nervous system tumours, particularly high-grade glioma, has been seriously questioned [72,73]. In the Deltour et al. [70] article on cancer incidence in the Nordic countries Sweden accounted for about 40% of the population and cases. Thus, under-reporting of brain tumour cases to the Swedish Cancer Register would make the conclusions of the Deltour et al. study less valid.

Little et al. [71] 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 [9] and our pooled results published in 2011 [28]. 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 paper version 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 Figs. 2–4 in the article by Little et al. [71], 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 ≥18 years and all 12 SEER registries. Thereby numerous assumptions were made as pointed out by Kundi [74] and Davis et al. [75].

Using only men, as Little et al. [71] did, ignores the fact that women had less frequent use of mobile phones than men in our studies, Table 10. 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 [28,41]. Thus, the age group 60–64 year old men is not valid to use for these calculations.

Little et al. [71] do not explain how they obtained different results on incidence trends based on the Hardell group results and Interphone on the risk for mobile phone use. They ignored that the Hardell group assessed also use of cordless desktop phones in contrast to Interphone. As pointed out by IARC and the Hardell group the appropriate exposure category for wireless phone RF-EMF is use of both mobile and cordless phones [1]. We have compared our results with Interphone regarding different age groups and exposure categories in these studies. Thereby the results are similar for both study groups [14]. We have now updated the results based on our 2011 publication, Table 11 [14]. We restricted cases and controls to the age group 30–59 years and disregarded use of cordless phones as in Interphone. Odds ratios are in fact somewhat lower in our study than in Interphone. It is thus remarkable that the projected incidence rates by Little et al. are so different based on our results compared with Interphone although ORs are similar. It should be added that Little et al. [71] present

Table 10
Gender and age distribution for use of mobile phones among glioma cases aged 20–80 years in the Hardell group studies [28]; $n = 1148$.

| Age, diagnosis | Men | | Women | | Total | |
|---|---|---|---|---|---|---|
| | 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%) |

wrong latency periods for the results in our studies both in the publication and in the web appendix.

There are several other points that may be added. The results by Little et al. [71] for oligodendroglioma >10 year latency in our study are wrong in the web appendix, should be OR = 2.2, 95% CI = 0.9–5.4 and not OR = 1.4, 95% CI = 0.9–2.3. Another example is that the results for anatomical localisations and tumour 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 groups, see Table 10. Furthermore, in the final Interphone Study Group [9] publication only results for the whole glioma group were presented in contrast to our published results for both low-grade and high-grade astrocytoma [27], results that are ignored by Little et al. We have now analysed the data further using our 2011 publication, Table 12 [28]. Obviously the risk is higher for high-grade (mostly glioblastoma multiforme) than low-grade astrocytoma for latency time >10 years. This is of interest considering the statistically significant yearly increasing incidence of high-grade glioma in the SEER data for 1992–2008, +0.64%, 95% CI = +0.33 to 0.95% published by Little et al. [71] without any further comments. On the contrary, the incidence of low-grade glioma decreased with −3.02%, 95% CI = −3.49 to −2.54%. Increasing yearly trend for glioma in the temporal lobe, +0.73%, 95% CI = +0.23 to 1.23% was also found [71]. Certainly these findings should have been explored in more detail in the study.

In summary the conclusion by Little et al. that "*Raised risk of glioma with mobile phone use, as reported by one (Swedish) study. . .are not consistent with observed incidence trends in the US population data. . .*" goes far beyond scientific evidence and what would be possible to show with the faulty methods used in the study. We agree with Kundi [74] that there is much room for improvement of the BMJ review process, as we have exemplified [54] regarding another recent BMJ publication by Frei et al. [61], as also discussed above.

One should be careful about using data on the incidence of brain tumours, like in Aydin et al. [53] and Deltour et al. [70], to dismiss results in analytical epidemiology. There might be other factors that influence the incidence rate like changes in exposure to other risk factors for brain tumours that are not assessed in descriptive studies. Cancer incidence depends on initiation, promotion and progression of the disease [76]. The mechanism for RF-EMF carcinogenesis is unclear which adds to the view that descriptive data on brain tumour incidence are of limited value.

There are in fact other studies that show an increasing incidence of brain tumours. In Australia the incidence of

Table 11
Odds ratio (OR) and 95% confidence interval (CI) for glioma in the Interphone study [9] and Hardell et al. [14] for the age group 30–59 years. Use of cordless phones disregarded in the Hardell group studies as was done in Interphone. Numbers of exposed cases (Ca) and controls (Co) are given.

| | Interphone Appendix 2 | | | Hardell et al. | | |
|---|---|---|---|---|---|---|
| | Ca/Co | OR | 95% CI | Ca/Co | OR | 95% CI |
| Unexposed[a] | 93/159 | (1.0) | – | 241/660 | (1.0) | – |
| *Latency* | | | | | | |
| 2–4 years | 460/451 | 1.68 | 1.16–2.41 | 128/322 | 1.09 | 0.84–1.41 |
| 5–9 years | 468/491 | 1.54 | 1.06–2.22 | 121/258 | 1.11 | 0.84–1.47 |
| 10+ years | 190/150 | 2.18 | 1.43–3.31 | 84/103 | 1.75 | 1.23–2.50 |

[a] Unexposed Interphone Appendix 2: Latency 1–1.9 years; unexposed Hardell et al.: No use + latency ≤ 1 year.

Table 12
Odds ratio (OR) and 95% confidence interval (CI) for mobile phone use and astrocytoma, cf. Hardell et al. [28].

| | >1–5 year latency | | >5–10 year latency | | >10 year latency | | Total, >1 year latency | |
|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Astrocytoma, high grade ($n = 820$) | 1.2 | 0.9–1.5 | 1.5 | 1.1–1.9 | 3.0 | 2.1–4.2 | 1.5 | 1.2–1.8 |
| Astrocytoma, low grade ($n = 132$) | 1.4 | 0.8–2.2 | 1.3 | 0.7–2.4 | 1.7 | 0.7–4.0 | 1.4 | 0.9–2.2 |

primary brain tumours was studied in two areas, the state of New South Wales and Australian Capital Territory, with about 7 million inhabitants [77]. The study covered the time period 2000–2008 and all diagnoses had a histopathological verification. It included 13 pathology databases servicing 24 neurosurgical centres. Adults aged ≥65 years recorded the largest proportion of malignant brain tumours, 52%. The Annual Percentage Change (APC) for malignant tumours increased statistically significant +3.9%, 95% CI +2.4 to 5.4%. An increase was seen among both men and women. The APC for benign tumours 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 tumours 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 [78]. No results were given for different tumour types, e.g. malignant and benign brain tumours, or anatomical site. The authors concluded that "*The study did not support an association between cellular telephone use and increased risk of brain and nervous tumours.*" However, that statement goes far beyond what is scientifically justified from this register based study and what was actually investigated.

Certainly it is more informative to analyse incidence trends by anatomical site and histology of the tumour. de Vocht et al. [79] reported in England for the time period 1998–2007 a statistically significant increasing incidence of brain tumours, the majority glioma, in the temporal lobe for men ($p < 0.01$) 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.

Zada et al. [80] studied incidence trends of primary malignant brain tumours in the Los Angeles area during 1992–2006. APC was calculated for microscopically confirmed histological subtypes and anatomic sub sites. The overall incidence of primary malignant brain tumours decreased over the time period with the exception of glioblastoma multiforme (astrocytoma WHO grade IV). The annual age adjusted incidence rate of that tumour type increased statistically significant in the frontal lobe with 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% ($p < 0.001$). In the parietal and occipital lobes or in overlapping lobes no statistically significant changes in incidence were seen. 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. These results by Zada et al. [80] are of interest since the highest absorbed dose of RF-EMF emissions from mobile phones has been calculated to occur in these parts of the brain [6].

It should be noted that also Deltour et al. [70] 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%. Unfortunately no data were given for subtypes of glioma and anatomical sites of the tumours, which would certainly have been informative. The authors did not consider these and other limitations when they conclude that "*Our data indicate that, so far, no risk associated with mobile phone use has manifested in adult glioma incidence trends...many increased or decreased risks reported in case-control studies are implausible, implying that biases and errors in the self-reported use of mobile phone have likely distorted the findings.*" It should be noted that regarding Sweden we reported increasing incidence of astrocytoma WHO grades I–IV during 1970–2007. In the age group >19 years the annual change was +2.16%, 95% CI +0.25 to 4.10% during 2000–2007 [41].

## 4. Discussion

The most comprehensive results on use of wireless phones and the association with brain tumours come from the Hardell group in Sweden and the international Interphone study. As pointed out by IARC [1] other studies as discussed above are too small with short latency times, usually in the range of at most 5 years. Both the Hardell group studies and Interphone give results for latency time of 10 years or more. Thus, a summary evaluation will mainly be based on results from these two 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. Cases were ascertained from Regional Cancer Registries in the Hardell group studies and all diagnoses were based on histopathological verification. Thus, all cases had been operated or undergone biopsy of the tumour for diagnosis. In contrast, in Interphone cases were identified from neurological or neurosurgical facilities in the

study regions; in some centres also from cancer registries. The diagnoses of glioma, meningioma and acoustic neuroma were based on histopathology or diagnostic imaging. It should be pointed out that the diagnosis of both meningioma and acoustic neuroma has a rather high precision using CT and/or MRI. Regarding glioma it is certainly more difficult to establish a valid diagnosis without histopathology, especially when it comes to subgroups such as different grades of astrocytoma (WHO grades I–IV). In the publication by Lahkola et al. [81] most glioma diagnoses were based on histopathology, whereas this has not been published for Interphone in total. It is notable that Interphone [9] has not presented separate results for astrocytoma in total in contrast to the Hardell group. Especially results for high-grade glioma including the most common glioma type, glioblastoma multiforme (WHO grade IV), would be of value since the highest risk was found for that subtype by Hardell et al., Table 12 [27,28]. It is also of interest that we found higher risk for use of mobile and cordless phones for astrocytoma grades III–IV than for grades I–II [82]. Some results were published for glioblastoma multiforme from the 5 North European countries [81]. Certainly the total result for glioma and >10 years since first ipsilateral mobile phone use with OR = 1.39, 95% CI = 1.01–1.92 ($p$ for trend 0.04) would have been of interest for glioblastoma multiforme separately in Lahkola et al. [81].

The Hardell group included cases aged 20–80 years whereas eligible cases in Interphone were aged 30–59 years at diagnosis. This difference is important since the highest incidence of astrocytoma WHO grade IV (glioblastoma multiforme) is found in the age group 45–75 years with mean age 61 years and 80% older than 50 years [83]. As can be seen in Table 10, the highest prevalence of use of mobile phones in the Hardell group studies was up to the age of 54 years, so limiting the age to 59 years as in Interphone diminishes the possibility to find an increased risk taking a reasonable tumour induction period. It seems as if the age distribution in Interphone was more decided by prevalence of mobile phone use in the population than age distribution for glioma cases. Excluding the age group 20–29 years, as in Interphone, makes also an evaluation of young users more difficult, see Table 9.

Meningioma is a slow growing benign tumour with a peak incidence in the sixth and seventh decade of life with a 3:2–2:1 female:male ratio [84]. As pointed out by Interphone [10] the incidence peak of acoustic neuroma is in the age group 50–65 years. Thus, again limiting upper age to 59 years for cases in Interphone excluded a large proportion of cases with meningioma or acoustic neuroma taking a reasonable latency period.

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. The register covers the whole population and each person is assigned a unique id-number making it possible to trace current address for all inhabitants. In Interphone one control was selected for each case from a 'locally appropriate population-based sampling frame'. In Germany the centres used individual matching or frequency matching. The matching variables were age within 5 years, gender and region of residence; in Israel also ethnic origin. When stratified matching was used individual matching was made afterwards from the whole control sample with cases being assigned one control subject (two in Germany) interviewed as close as possible in time to the case [9]. 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.

The Nordic countries have population registers that were used in Denmark, Norway and Finland for recruitment of controls in Interphone. Also Germany used a population register [85]. However, UK used general practioners' lists [86] and in Japan random digit dialling was used [44,87]. Certainly the methods used in Interphone may introduce selection bias. Patient lists are usually selective to use for drawing of controls and do not represent the whole population which is the source of the cases. Also random digit dialling has the potential to introduce selection bias since persons that are registered to subscribe a phone are usually wealthier than non-subscribers. Furthermore, it seems not to be the most appropriate method for selection of controls in a study on mobile phone use, and certainly not regarding cordless phones, since phone subscribers are selected as controls. Furthermore, later selection of controls from a pool with individual matching may give the possibility for selection bias if this is not done in a blinded manner as to exposure status.

These methods contrast to the Hardell group where controls were drawn consequently to the cases and all controls that answered the questionnaire were included in the analyses. In Interphone proxy interviews were performed for 13% of glioma cases but only 1% of controls [9]. This is in contrast to the Hardell group study on deceased cases with malignant brain tumours [26]. Deceased controls were drawn from the Death Registry in Sweden. Relatives to both deceased cases and deceased controls were interviewed, thereby creating the same condition for assessment of exposure among cases and controls. Although using proxy interviews for both cases and controls is the more appropriate method exclusion of proxy interviews in Interphone had little impact on the overall result in the sensitivity analysis.

Use of wireless phones was 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. 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 for both sides. This information was checked during the supplementary phone calls. 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. There was a very good agreement of the results using these three methods to assess these data. Also

other exposures were assessed in the questionnaire. 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 on the individual.

We investigated in more detail the possibility of recall and observational bias in our second case-control study [21]. Reporting a previous cancer or if a relative helped to fill in the questionnaire did not change the results, i.e., were no confounding factors. Potential observational bias during phone interviews was analysed by comparing change of exposure in cases and controls after these interviews. No statistically significant differences were found, showing that our results could not be explained by observational bias, for further details see discussion in that publication [21].

On the contrary information on past mobile phone use was mostly 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. In the personal interviews a computer program that guided the interview with questions read by the interviewer from a laptop computer screen was used. The interviews in the Swedish part lasted for about 45 min. The answers were entered directly into the computer by the interviewer. Cards were shown to if possible identify the model of the mobile phone [88]. The purpose of the study was thereby obviously disclosed to the cases and controls. This was in contrast to the Hardell group mailed questionnaire that contained a large number of other questions without special attention to wireless phones.

We regard hospital based interviews of cases, as in the Interphone study, to be a major disadvantage and ethically questionable. At that time the patient has not fully recovered from e.g. surgery, may not have been fully informed about the diagnosis, treatment and prognosis and may even be under sedation by drugs. Using computer based face-to-face interviews may also be a stressful situation for the patient. 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 [89]. Obviously observational bias could have been introduced by the interview methods in Interphone. Only Finland used a paper version of the questionnaire, but Finland has never published country specific results on the different tumour types, which would certainly have been of interest. For unclear reasons the results on glioma were only included as part of the results for the 5 North European countries [81] and as part of the whole Interphone study [9]. 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?

It should be noted that the number of participating cases and controls from each centre in Interphone was quite low. It varied for glioma from 60 (Japan) to at most 421 (UK North), for meningioma from 52 (New Zealand) to 350 (Israel) and for acoustic neuroma from 18 (New Zealand) to 152 (UK South). Similarly the number of controls varied according to centre [9,10]. It is obvious that with so low number of interviewed subjects by many different interviewers the quality may have been hampered in Interphone by low training and experience of certain interviewers. 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$1640 h 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. In the Hardell group studies few persons conducted all interviews of the 1251 participating cases with malignant brain tumour, 1254 cases with benign brain tumour, and 2438 controls (total 4942; note one case had both a malignant and a benign brain tumour). 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. The higher risk restricting analysis to 'experienced interviewers' in Interphone indicates observational bias during assessment of exposure decreasing the risk. Furthermore, 20 interviews as the definition was in Interphone to be an experienced interviewer, is after all a very low number.

Several other sensitivity analyses were performed in Interphone without any major impact on the results. It is discussed in the Interphone study [9] that the increased risk for glioma in the highest decile of cumulative exposure was caused by a number of subjects reporting >5 h call time per day. This number may be real in e.g. certain occupations using the phone as a working tool. Furthermore, if call time was truncated to 5 h per day no statistically significant difference of the risk was found, OR = 1.38, 95% CI = 1.02–1.87 for glioma and OR = 3.03, 95% CI = 1.62–5.67 for acoustic neuroma (exposure up to 5 years before reference date). Certainly it is not justified to exclude these subjects from the analysis as was done in some of the calculations in Interphone [9,10].

It is always essential to have a high response rate in case-control studies to get as valid results as possible. In the Hardell group studies the response rate was 85% ($n$ = 1251) for cases with malignant brain tumour, 88% ($n$ = 1254) for cases with benign brain tumour, and 84% ($n$ = 2438) for controls [29,40]. Lower response rates were obtained in the Interphone study, 64%, range by centre 36–92%, ($n$ = 2765) for glioma cases, 78%, range 56–92%, ($n$ = 2425) for meningioma cases, 82%, range 70–100% ($n$ = 1121) for acoustic neuroma cases, and 53%, range 42–74%, ($n$ = 7658) for controls [9,10]. Certainly these low response rates, less than half of the cases and controls in some centres, may have created the possibility of considerable selection bias and are examples of the multiple methodological problems in Interphone. As has been

discussed elsewhere not responding controls in Interphone tended to be less frequent users of mobile phone than participating controls leading to underestimation of the risk [32].

There are other differences between the Hardell group studies and Interphone study such as restricting age to 30–59 years in Interphone compared with 20–80 years in the Hardell-group studies and considering use of cordless phones as no exposure to RE-EMF in Interphone. Even if the prevalence of mobile phone use is highest in the age group 30–59 years, excluding older cases diminishes the possibility to find an increased risk, assuming a reasonable latency time. As discussed above the peak incidence of most brain tumours is at a higher age. In a case series from Canada all brain tumours showed a bimodal age distribution with one peak in the 0–4 age group and the other in the 60–69 age group [90]. As shown elsewhere [14] step-wise exclusion of the age group 20–29 years, 60–80 years and including cordless phone use among unexposed reduced OR in the Hardell-group studies to similar results as in Interphone [see Tables 1 and 2 in the publication]. Thus, Interphone seems to have underestimated the risk also for these reasons.

Survival of patients with glioma has only been presented by the Hardell group [68]. Decreased survival of glioma cases with long-term and high cumulative use of wireless phones was found. We found a survival disadvantage for astrocytoma WHO grade IV among cases using mobile phone or cordless phone indicating a worse prognosis in that patient group. On the contrary, a survival benefit for astrocytoma WHO grades I–II was observed. The fact that there was no clear trend with intensity or duration of wireless phone use for low-grade astrocytoma does not speak in favour of an effect of RF-EMF from such use. The exposure might, however, produce awareness bias in these cases. RF-EMF may give tumour promotion [91] inducing disease related personality disturbances and habit changes leading to earlier tumour diagnosis than among unexposed patients. This would result in earlier treatment with a better prognosis after surgery in this patient group [69]. These findings indicate a complex biological effect from RF-EMF exposure and strengthen a causal association between these tumour types, e.g. astrocytoma WHO grade IV (glioblastoma multiforme), and use of wireless phones.

By placing a strong emphasis on incidence data an association between use of wireless phones and brain tumours has been challenged [92]. 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 tumours, for which there seemed to be little evidence. This belief is unfounded for two reasons. The first relates to latent periods for glioma and acoustic neuroma development, typically 10–40 years [93,94]. The results on long-term use of wireless phones are scanty and at most latency period of 10+ years have been studied. Furthermore, we know little about the earliest events in the genesis of glioma in humans for obvious reasons. However, progression of glioma has been studied in large series of tumours of different malignancy grades. Patients with low-grade glioma have been followed with later progression to high-grade glioma [95]. Thus, since 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 incompatible with a tumour initiating effect. An initiating effect is what would have the most direct effect on the incidence. The other reason concerns the possibility of an effect on tumour development (promotion) and its consequences on the increase in incidence that can possibly occur. If the exposure acts as a promoter, this would decrease latency time for already existing tumours, giving a temporary but not a continuous increase in incidence. In addition it has to be pointed out that any such effect on tumour development is limited by the magnitude of the shift of the age-incidence function and its slope for the respective tumour type [91]. It should be noted that studies on tumour type and anatomical localisation indicate by now an effect from RF-EMF on the incidence of brain tumours [71,77,79,80].

## 5. Conclusions

There is a consistent pattern of increased risk of glioma and acoustic neuroma associated with use of mobile phones and cordless phones. The epidemiological evidence comes mainly from two study centres, the Hardell group and the Interphone study group. In the same studies by the Hardell group and Interphone study group no consistent pattern of an increased risk was found for meningioma. These results strengthen the other findings, i.e., increased risk for glioma and acoustic neuroma, since a systematic bias in the studies would also have been inherit for meningioma. Furthermore, a causal association between use of mobile phone and glioma and acoustic neuroma comes from the meta-analyses as presented in this publication and also reviewed elsewhere [96]. Supportive evidence comes also from anatomical localisation of the tumour to the most exposed area of the brain, cumulative exposure and latency time that all add to the biological relevance of an increased risk. In addition risk calculation based on estimated absorbed dose gives strength to the findings as well as the impact on survival of glioma patients relating to their use of mobile and cordless phones.

Evidence is increasing that workers with heavy use of wireless phones who develop glioma or acoustic neuroma should be compensated. In fact, the first case with such compensation has now been established in court. The Italian Supreme Court affirmed a previous ruling that the Insurance Body for Work (INAIL) must grant worker's compensation to a businessman who had used wireless phones for 12 years and developed a neuroma in the brain (www.applelettrosmog.it; 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 neuroma was located in the trigeminal Gasser's ganglion in the brain. This fifth cranial nerve controls facial sensations and muscles. It is

the same type of tumour as the acoustic neuroma in the eighth cranial nerve located in the same area of the brain. The Italian case fulfils the criteria for a causal association; more than 10 years use of wireless phones, high cumulative exposure on the same side as the tumour appeared, and a tumour type that would be predicted based on previous research on use of wireless phones and brain tumour risk. No further appeal of the Supreme Court decision is possible.

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. The current 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.

## Acknowledgements

Supported by grants from Cancer-och Allergifonden, Cancerhjälpen, and Örebro University Hospital Cancer Fund.

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