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# Mobile phone and cordless phone use and the risk for glioma – Analysis of pooled case-control studies in Sweden, 1997–2003 and 2007–2009

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## Abstract

We made a pooled analysis of two case-control studies on malignant brain tumours with patients diagnosed during 1997–2003 and 2007–2009. They were aged 20–80 years and 18–75 years, respectively, at the time of diagnosis. Only cases with histopathological verification of the tumour were included. Population-based controls, matched on age and gender, were used. Exposures were assessed by questionnaire. The whole reference group was used in the unconditional regression analysis adjusted for gender, age, year of diagnosis, and socio-economic index. In total, 1498 (89%) cases and 3530 (87%) controls participated. Mobile phone use increased the risk of glioma, OR = 1.3, 95% CI = 1.1–1.6 overall, increasing to OR = 3.0, 95% CI = 1.7–5.2 in the >25 year latency group. Use of cordless phones increased the risk to OR = 1.4, 95% CI = 1.1–1.7, with highest risk in the >15–20 years latency group yielding OR = 1.7, 95% CI = 1.1–2.5. The OR increased statistically significant both per 100 h of cumulative use, and per year of latency for mobile and cordless phone use. Highest ORs overall were found for ipsilateral mobile or cordless phone use, OR = 1.8, 95% CI = 1.4–2.2 and OR = 1.7, 95% CI = 1.3–2.1, respectively. The highest risk was found for glioma in the temporal lobe. First use of mobile or cordless phone before the age of 20 gave higher OR for glioma than in later age groups.

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**Keywords:** Ipsilateral; 25 years latency; Time since first exposure; Glioma; Wireless phones

## 1. Introduction

There has been a large worldwide increase during the last decade in the use of wireless communication, with greater exposure to radiofrequency electromagnetic fields (RF-EMF). This has caused increasing concern for health risk. During use of both mobile and cordless phones, the brain is the main target of RF-EMF. The highest exposure is on the same side of the brain when the handheld phone is used (ipsilateral), whereas the contralateral side is less exposed [1]. Due to the smaller head size, thinner skull bones and higher brain conductivity, a child absorbs higher rates than adults [2–4].

Our group reported the first indication of an increased brain tumour risk associated with use of wireless phones some

15 years ago [5–7]. This was followed by additional case-control studies as reviewed in Hardell et al. [8]. A Danish cohort study on mobile phone users has been initiated [9], but poor exposure assessment makes it uninformative [10,11].

The International Agency for Research on Cancer (IARC) at WHO evaluated human cancer risks from RF-EMF exposure in May 2011. It included all sources in the frequency range of 30 kHz–300 GHz. A total of 29 invited scientists participated. The final classification as Group 2B means that RF-EMF exposure is ‘possibly’ a human carcinogen, a conclusion based on an overwhelming majority of the voting experts [10,12].

The evaluation on the long-term use of wireless phones, i.e. >10 years, were in the IARC classification based on our results [13–15] and the Interphone study group, also preprint studies available [16–18]. The brain tumours associated with the use of wireless phones are the malignant types, mostly

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glioma, and acoustic neuroma, a benign tumour of the 8th cranial nerve. In contrast, no consistent pattern of an association has been found for the most common benign brain tumour, meningioma [see also reviews in [8,19,20]. The Interphone results were reported only on the use of mobile phones, whereas we also included cordless phones in our assessment. The potential bias due to this different classification of exposure that distorts of the overall risk towards unity has been discussed elsewhere [8,21].

The IARC evaluation was based on fairly short latency period (time from first exposure until diagnosis), with results on at most the latency group  $\geq 10$  years. To study longer periods of use, we made a new case-control study encompassing patients diagnosed from 2007 to 2009. Data have already been published on acoustic neuroma [22], meningioma, [23] and malignant brain tumours in total [24].

To enlarge the study group, we have now pooled our results on malignant brain tumours for 1997–2003 and 2007–2009, because the same methods were used for both periods. We present in the following results for the most common type of malignant brain tumour, glioma. It is of importance to present separate results on glioma to compare our results with Interphone [16]. Also, separate analysis of other malignant brain tumour types is presented. The ethics committee approved these studies.

## 2. Materials and methods

Detailed information on materials and methods has been given previously [13,24]. In short, six administrative regions with oncology centres covering Sweden registered new cancer cases. For 1997–2003, cases and controls covered central Sweden [13], whereas the 2007–2009 study included the whole country [24]. The oncology centres reported new cases with histopathologically verified brain tumour, either benign or malignant, to us during these periods, although the actual reporting interval varied for centre to centre. Both men and women were included aged 20–80 years (1997–2003) and 18–75 years (2007–2009) at the time of diagnosis. Only living cases were included, each patient giving permission to the responsible physician before inclusion in the study. Tumour localisation in the brain was based on reports to the cancer registries and medical records, which were obtained after informed consent from the patients.

Controls were ascertained from the Swedish Population Registry, covering the whole country and being continuously updated, such that each person was traced by a unique ID number. The registry also records the address to each person. For each case, one control subject of the same gender in the same 5-year group was drawn at random from this registry. They were assigned the same year for cut-off of all exposure as the diagnosis of the each case. All these controls were used in the analysis of risk of glioma.

Exposure was assessed using a mailed questionnaire sent to each person. Regarding use of a mobile phone, the time

of average use (min per day) was estimated. The technology has changed since the first introduction of mobile phones. The first generation was analogue phones with an output power of 1 W at about 900 MHz followed by the 2nd generation GSM phones (2G) with either 900 or 1800 MHz frequency and with a pulsed output power. The mean output power was of the order of tens of mW. In the 3rd generation phones (3G) the output is more to be characterised as amplitude modulated than pulsed and the output power is of the order of tens of  $\mu$ W. The type of mobile phone was recorded and checked by the prefix for the phone number; 010 for analogue phones and 07 for digital phones (2G, 3G).

Some special questions covered the extent of use in a car with an external antenna, and use of a hands-free device, both regarded as non-exposure to RF-EMF. The ear mostly used during phone calls, or equally both ears, was also noted.

Use of cordless desktop phones was covered by similar questions; years, average daily use, use of a hands-free device, and preferred ear. The procedure was conducted without knowledge of case/control status. Use of the wireless phone was referred to as ipsilateral ( $\geq 50\%$  of the time) or contralateral ( $< 50\%$  of the time) in relation to tumour side. The same method was also applied for the control group; the subjects were assigned the same ‘tumour’ side as the respective case to the matched control.

The questionnaire also contained a number of questions relating to the overall working history, exposure to different chemicals and other agents, smoking habits, X-ray investigations of the head and neck, and heredity traits for cancer. These other exposure factors will be published separately for the whole study period. When questionnaire answers were unclear, they were resolved by phone using trained interviewers. Thereby, a written protocol was used for clarification of each question. The interviewer supplemented the whole questionnaire during the phone call. Each questionnaire had received a unique ID number that did not disclose whether it was a case or a control; i.e. the interviewer was unaware of the status during further data processing. All information was coded and entered into a database. Case or control status was not disclosed until statistical analyses were undertaken.

We made in addition a separate case-control study on deceased cases during for 1997–2003, using deceased persons as reference entities by interviewing the next of kin [25], see discussion below. These cases and controls are not included in the present study.

### 2.1. Statistical methods

StataSE 12.1 (Stata/SE 12.1 for Windows; StataCorp., College Station TX) was used for the analyses. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression including the whole control sample (i.e. matched to both malignant and benign cases) to increase the power of the study.

Latency (time from first use) was defined as the year of first use of a wireless phone to the year of diagnosis (the

Table 1  
Histopathology of all malignant brain tumours ( $n = 1498$ ).

| Histopathology                           | Men      |      | Women    |      | Total    |      |
|------------------------------------------|----------|------|----------|------|----------|------|
|                                          | <i>n</i> | %    | <i>n</i> | %    | <i>n</i> | %    |
| Glioma                                   | 817      | 92.9 | 563      | 91.0 | 1380     | 92.1 |
| -Astrocytoma grade I–II                  | 123      | 14.0 | 98       | 15.8 | 221      | 14.8 |
| –Grade I                                 | 14       | 1.6  | 20       | 3.2  | 34       | 2.3  |
| –Grade II                                | 109      | 12.4 | 78       | 12.6 | 187      | 12.5 |
| -Astrocytoma grade III–IV <sup>a,b</sup> | 540      | 61.4 | 317      | 51.2 | 857      | 57.2 |
| –Grade III <sup>a</sup>                  | 105      | 11.9 | 55       | 8.9  | 160      | 10.7 |
| –Grade IV <sup>a,b</sup>                 | 434      | 49.4 | 260      | 42.0 | 694      | 46.3 |
| -Oligodendroglioma                       | 71       | 8.1  | 91       | 14.7 | 162      | 10.8 |
| -Other/mixed glioma                      | 83       | 9.4  | 57       | 9.2  | 140      | 9.3  |
| Medulloblastoma                          | 9        | 1.0  | 2        | 0.3  | 11       | 0.7  |
| Ependymoma <sup>c</sup>                  | 19       | 2.2  | 19       | 3.1  | 38       | 2.5  |
| Other malignant <sup>d</sup>             | 34       | 3.9  | 35       | 5.7  | 69       | 4.6  |
| Total, malignant                         | 879      |      | 619      |      | 1498     |      |

<sup>a</sup> One case had both an astrocytoma grade IV and a meningioma.

<sup>b</sup> Three cases had no information about specific grade (III or IV).

<sup>c</sup> One case had both an ependymoma and an acoustic neuroma.

<sup>d</sup> One case had both an other malignant tumour and an acoustic neuroma.

same years being used for the matched control). The cumulative number of hours of use was calculated (number of years multiplied by average time per year based on use per day). Use in a car with external antenna was disregarded, as was use of a hands-free device. A minimum latency period of  $\leq 1$  year of exposure was adopted, less than which was included in the unexposed category. The same year as for each case's diagnosis was used for the corresponding control as the cut-off for exposure accumulation. Note that latency was calculated separately for the respective phone type or combination of phones that were analysed.

Adjustment was made for the matching variables gender, age (as a continuous variable) and year of diagnosis. It was also made for socio-economic index (SEI) divided into four categories (blue-collar worker, white-collar worker, self-employed, unemployed), since an association between white-collar work and brain tumours was reported by Preston Martin and Mack in 1996 [26]. Latency was analysed using six periods,  $>1$ –5 years,  $>5$ –10 years,  $>10$ –15 years,  $>15$ –20 years,  $>20$ –25 years, and  $>25$  years. Cumulative use of the different phone types and combinations was analysed in quartiles based on the distribution of total use of wireless phones among the controls. Latency and cumulative use were also analysed as continuous variables (per year of latency, per 100 h cumulative use) to explore dose-response relationships. Laterality was not analysed for the whole group of wireless phone users, since the side could differ for mobile and cordless phone use by the same person.

Restricted cubic splines were used to display the relationship between cumulative use and latency of wireless phones with glioma. Adjustment was made for the same variables as in the logistic regression. Four knots were used at the 5th, 35th, 65th, and 95th percentiles, as suggested by Harrell [27]. *P*-values for non-linearity were estimated by testing whether

the coefficient of the second and third spline was equal to zero by using the Wald test.

### 3. Results

#### 3.1. Numbers

The number of reported cases from the oncology centres, as well as reasons for not inclusion in the study base, have been published for both study periods [13,24]. In total, 1691 cases fulfilling the inclusion criteria were enrolled. Of these cases, 1498 (89%) answered the questionnaire, of whom 879 were men and 619 women. The mean age was 52 (median 54, range 18–80). The histopathological distribution (Table 1) shows that most had a diagnosis of glioma,  $n = 1380$  (92%). Thus, the results are presented for the group of glioma cases, but also in brief for the other groups of malignant brain tumours.

Of the 4038 controls, 3530 (87%) participated, 1492 men and 2038 women. The mean age was 54 (median 55, range 19–80); further details are available in previous publications [13,24].

#### 3.2. Overall results and latency

The median latency time for use of mobile phones in glioma cases was 9.0 years (mean 10.1, range 2–28). The corresponding results for cordless phones were median 7.0 years (mean 8.0, range 2–21). The results are shown in Table 2 for glioma and the use of wireless phones in different latency groups. Analogue phones gave OR = 1.6, 95% CI = 1.2–2.0, increasing to OR = 4.8, 95% CI = 2.5–9.1 in the latency group of  $>25$  years. Note that the latency time was counted from

Table 2

Odds ratio (OR) and 95% confidence interval (CI) for glioma ( $n = 1380$ ) for use of mobile and cordless phones in different latency groups. Numbers of exposed cases (Ca) and population-based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

| Latency                               | Analogue                    | Digital (2G)                 | Digital (UMTS, 3G)          | Mobile phone, total          | Mobile phone, digital (2G, 3G) | Cordless phone               | Digital type (2G, 3G, cordless) | Wireless phone                |
|---------------------------------------|-----------------------------|------------------------------|-----------------------------|------------------------------|--------------------------------|------------------------------|---------------------------------|-------------------------------|
|                                       | OR, CI (Ca/Co)              | OR, CI (Ca/Co)               | OR, CI (Ca/Co)              | OR, CI (Ca/Co)               | OR, CI (Ca/Co)                 | OR, CI (Ca/Co)               | OR, CI (Ca/Co)                  | OR, CI (Ca/Co)                |
| <b>Glioma (<math>n = 1380</math>)</b> |                             |                              |                             |                              |                                |                              |                                 |                               |
| Total >1 year                         | 1.6<br>1.2–2.0<br>(299/558) | 1.3<br>1.1–1.6<br>(884/2014) | 2.0<br>0.95–4.4<br>(58/141) | 1.3<br>1.1–1.6<br>(945/2148) | 1.3<br>1.1–1.6<br>(885/2019)   | 1.4<br>1.1–1.7<br>(752/1724) | 1.3<br>1.1–1.6<br>(1037/2393)   | 1.3<br>1.1–1.6<br>(1074/2472) |
| >1–5 years                            | 1.1<br>0.7–1.7<br>(34/87)   | 1.2<br>0.99–1.5<br>(283/714) | 1.9<br>0.9–4.1<br>(46/127)  | 1.2<br>0.98–1.5<br>(262/674) | 1.2<br>0.99–1.5<br>(284/719)   | 1.3<br>1.1–1.6<br>(271/653)  | 1.2<br>0.9–1.4<br>(295/796)     | 1.1<br>0.9–1.4<br>(271/748)   |
| >5–10 years                           | 1.1<br>0.8–1.6<br>(56/137)  | 1.7<br>1.3–2.2<br>(314/659)  | 4.1<br>1.3–12<br>(12/14)    | 1.5<br>1.2–1.8<br>(301/688)  | 1.7<br>1.3–2.2<br>(314/659)    | 1.4<br>1.1–1.8<br>(294/655)  | 1.6<br>1.3–2.0<br>(363/758)     | 1.5<br>1.2–1.9<br>(351/767)   |
| >10–15 years                          | 2.2<br>1.5–3.2<br>(71/113)  | 1.4<br>1.04–1.9<br>(189/471) | –<br>(0/0)                  | 1.4<br>1.1–1.9<br>(211/476)  | 1.4<br>1.04–1.9<br>(189/471)   | 1.4<br>1.1–1.9<br>(131/294)  | 1.4<br>1.1–1.9<br>(242/584)     | 1.4<br>1.1–1.8<br>(248/578)   |
| >15–20 years                          | 2.4<br>1.5–3.7<br>(59/107)  | 2.1<br>1.5–3.0<br>(98/170)   | –<br>(0/0)                  | 1.6<br>1.1–2.2<br>(92/196)   | 2.1<br>1.5–3.0<br>(98/170)     | 1.7<br>1.1–2.5<br>(50/109)   | 2.0<br>1.5–2.8<br>(131/242)     | 1.7<br>1.2–2.3<br>(121/253)   |
| >20–25 years                          | 3.2<br>1.9–5.5<br>(50/81)   | –<br>(0/0)                   | –<br>(0/0)                  | 2.1<br>1.3–3.2<br>(50/81)    | –<br>(0/0)                     | 1.4<br>0.5–3.8<br>(6/13)     | 1.6<br>0.6–4.4<br>(6/13)        | 1.9<br>1.3–2.9<br>(54/93)     |
| >25 years                             | 4.8<br>2.5–9.1<br>(29/33)   | –<br>(0/0)                   | –<br>(0/0)                  | 3.0<br>1.7–5.2<br>(29/33)    | –<br>(0/0)                     | –<br>(0/0)                   | –<br>(0/0)                      | 3.0<br>1.7–5.2<br>(29/33)     |

Table 3

Odds ratio (OR) and 95% confidence interval (CI) for glioma per 100 h cumulative use and per year of latency. Adjustment was made for age at diagnosis, gender, SEI-code and year for diagnosis. Population based controls were used.

|                                 | Per 100 h cumulative use |             | Per year of latency |             |
|---------------------------------|--------------------------|-------------|---------------------|-------------|
|                                 | OR                       | 95% CI      | OR                  | 95% CI      |
| Analogue                        | 1.043                    | 1.026–1.061 | 1.055               | 1.036–1.075 |
| Digital (2G)                    | 1.014                    | 1.009–1.018 | 1.035               | 1.014–1.057 |
| Digital (UMTS, 3G)              | 1.047                    | 1.002–1.093 | 1.157               | 0.994–1.345 |
| Mobile phone, total             | 1.013                    | 1.009–1.017 | 1.032               | 1.017–1.046 |
| Cordless phone                  | 1.014                    | 1.008–1.019 | 1.027               | 1.009–1.046 |
| Digital type (2G, 3G, cordless) | 1.011                    | 1.008–1.014 | 1.035               | 1.017–1.053 |
| Wireless phone                  | 1.011                    | 1.008–1.014 | 1.032               | 1.019–1.046 |

the first use of the specific telephone type; for instance, a 2G digital phone user may have previously used an analogue phone.

Use of digital 2G phones gave overall OR = 1.3, 95% CI = 1.1–1.6 increasing to OR = 2.1, 95% CI = 1.5–3.0 with a latency >15–20 years, the longest latency interval. The results for digital 3G phones showed highest risk in the >5–10 years latency group, OR = 4.1, 95% CI = 1.3–12. This was the longest latency group for 3G use since the technology is new; the calculations were based on small numbers.

Digital type of mobile phones (2G, 3G) gave in total OR = 1.3, 95% CI = 1.1–1.6, increasing to OR = 2.1, 95% CI = 1.5–3.0 in the longest latency group (>15–20 years).

Use of cordless phones gave OR = 1.4, 95% CI = 1.1–1.7, with highest risk in the latency group >15–20 years, OR = 1.7, 95% CI = 1.1–2.5. Few subjects were included in the latency group >20–25 years.

The digital type of wireless phones (2G, 3G, and/or cordless phone) gave OR = 1.3, 95% CI = 1.1–1.6, increasing to OR = 1.6, 95% CI = 1.3–2.0 in the latency group >5–10 years, then tending to drop, and again increasing to OR = 2.0, 95% CI = 1.5–2.8 risk in the latency group >15–20 years.

The group of total wireless phone use (mobile phone and/or cordless phone) gave similar results to mobile phone use, with increasing risk with latency yielding highest risk in the longest latency group >25 years; OR = 3.0, 95% CI = 1.7–5.2.

The risk increased per additional year of latency given for wireless phones; OR = 1.032, 95% CI = 1.019–1.046 (Table 3).

### 3.3. Temporal lobe

Somewhat higher ORs were obtained for glioma localised in the temporal or overlapping lobes ( $n=505$ ). Thus, mobile phone use yielded OR = 3.6, 95% CI = 1.8–7.4 versus OR = 3.0, 95% CI = 1.7–5.2 in total in the >25 years latency group (data not in Table). The results for cordless phone in the >20–25 years latency group were OR = 2.1, 95% CI = 0.6–7.0 versus OR = 1.4, 95% CI = 0.5–3.8, respectively.

The corresponding results for glioma in the temporal lobe only ( $n=367$ ) were OR = 4.3, 95% CI = 2.0–9.3 for mobile phones and OR = 2.4, 95% CI = 0.6–9.5 for cordless phones

(data not in Table). Wireless phone use in total in the >25 year latency group gave OR = 3.7, 95% CI = 1.8–7.4 for glioma in temporal or overlapping lobes, increasing to OR = 4.2, 95% CI = 1.9–9.1 for glioma localised only in temporal lobe.

### 3.4. Laterality

For all phone types, ipsilateral use was associated with the highest risk (Table 4). Ipsilateral mobile phone use gave OR = 1.8, 95% CI = 1.4–2.2, whereas contralateral use gave OR = 1.1, 95% CI = 0.8–1.4. The same pattern of association was seen for cordless phones, OR = 1.7, 95% CI = 1.3–2.1 and OR = 1.2, 95% CI = 0.9–1.6, respectively.

These results are also given in Table 5 for the different latency groups. Regarding mobile phone use, highest risk was associated with ipsilateral use in the >25 year latency group, OR = 4.6, 95% CI = 2.1–10. Contralateral mobile phone use also gave a statistically significant increased risk in the longest latency group, although with a lower OR than for ipsilateral use. Higher ORs were also calculated for ipsilateral cordless phone use in the different latency groups, except for latency >20–25 years. However, these latter results were based on small numbers.

### 3.5. Laterality according to Inskip

Laterality was also analysed with the method described by Inskip [28]. Self-reported laterality of use of a mobile phone or cordless phone among cases with glioma was associated with statistically significant increased risk. Thus, the relative risk (RR) for use of mobile phone was 1.5,  $P < 0.001$  and for use of cordless phone RR = 1.4,  $P < 0.001$  (data not in Table).

### 3.6. Cumulative use

Cumulative use of wireless phones was analysed in quartiles, based on total use of wireless phones among the controls (Table 6). The cumulative time was counted for use of the specific phone in the different categories, including in “mobile phones” all types of mobile phones, and for “wireless phones” also the use of cordless phones. For all phone types except 3G, the highest risk with a statistically significant trend was in the 4th quartile. No statistically significant trend was found for

Table 4

Odds ratio (OR) and 95% confidence interval (CI) for glioma, total, ipsilateral, and contralateral exposure. Numbers of exposed cases (Ca) and population based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

|                     | All      |     |          | Ipsilateral |     |          | Contralateral |     |         |
|---------------------|----------|-----|----------|-------------|-----|----------|---------------|-----|---------|
|                     | Ca/Co    | OR  | 95% CI   | Ca/Co       | OR  | 95% CI   | Ca/Co         | OR  | 95% CI  |
| Analogue            | 299/558  | 1.6 | 1.2–2.0  | 190/252     | 2.0 | 1.5–2.7  | 98/184        | 1.3 | 0.9–1.9 |
| Digital (2G)        | 884/2014 | 1.3 | 1.1–1.6  | 550/865     | 1.8 | 1.4–2.2  | 298/684       | 1.1 | 0.8–1.4 |
| Digital (UMTS, 3G)  | 58/141   | 2.0 | 0.95–4.4 | 35/70       | 2.3 | 0.99–5.4 | 21/45         | 1.9 | 0.7–4.8 |
| Mobile phone, total | 945/2148 | 1.3 | 1.1–1.6  | 592/920     | 1.8 | 1.4–2.2  | 316/729       | 1.1 | 0.8–1.4 |
| Cordless phone      | 752/1724 | 1.4 | 1.1–1.7  | 461/766     | 1.7 | 1.3–2.1  | 259/565       | 1.2 | 0.9–1.6 |

Ipsilateral:  $\geq 50\%$  use of the phone on the same side as the tumour was located.

Contralateral:  $< 50\%$  use of the phone on the same side as the tumour was located.

Tumour laterality not available for 77 cases and 836 controls.

3G digital phones, but these results were also based on small numbers. Wireless phone total use ( $>1486$  h) gave OR = 2.0, 95% CI = 1.6–2.6 in the 4th quartile, with similar results for total mobile and cordless phone use.

ORs increased statistically significant per 100 h of cumulative use for all types of phones (Table 3). Wireless phone increased the risk with OR = 1.011, 95% CI = 1.008–1.014 per 100 h of cumulative use.

### 3.7. Multivariate analysis

Results are shown in Table 7 for multivariate analysis of OR and 95% CI per 100 h cumulative use. The risk increased statistically significant for the different phone types except 3G (UMTS). The risk per year of latency was also calculated,

adjusted for years of use of any mobile or cordless phone before the respective type. OR increased statistically significant for the different phone types, except for 3G yielding OR = 1.127, 95% CI = 0.955–1.329.

### 3.8. Age groups

The risks of glioma, based on different age groups for first use of wireless phones, are given in Table 8. Regarding mobile phone use, the highest OR was obtained for first use before the age of 20 years, OR = 1.8, 95% CI = 1.2–2.8. The risk increased for ipsilateral use to OR = 2.3, 95% CI = 1.3–4.2. Cordless phone gave OR = 2.3, 95% CI = 1.4–3.9 in total for the age group  $< 20$  years, increasing to OR = 3.1, 95% CI = 1.6–6.3 for ipsilateral use. Lower ORs were seen for

Table 5

Odds ratio (OR) and 95% confidence interval (CI) for glioma ( $n = 1380$ ) for ipsilateral and contralateral mobile, and cordless phone use in different latency groups. Numbers of exposed cases (Ca) and population-based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

| Latency                               | Mobile phone                 |                               |                                 | Cordless phone               |                               |                                 |
|---------------------------------------|------------------------------|-------------------------------|---------------------------------|------------------------------|-------------------------------|---------------------------------|
|                                       | Total<br>OR, CI (Ca/Co)      | Ipsilateral<br>OR, CI (Ca/Co) | Contralateral<br>OR, CI (Ca/Co) | Total<br>OR, CI (Ca/Co)      | Ipsilateral<br>OR, CI (Ca/Co) | Contralateral<br>OR, CI (Ca/Co) |
| <b>Glioma (<math>n = 1380</math>)</b> |                              |                               |                                 |                              |                               |                                 |
| Total, $>1$ year                      | 1.3<br>1.1–1.6<br>(945/2148) | 1.8<br>1.4–2.2<br>(592/920)   | 1.1<br>0.8–1.4<br>(316/729)     | 1.4<br>1.1–1.7<br>(752/1724) | 1.7<br>1.3–2.1<br>(461/766)   | 1.2<br>0.9–1.6<br>(259/565)     |
| $>1$ –5 years                         | 1.2<br>0.98–1.5<br>(262/674) | 1.6<br>1.3–2.1<br>(167/271)   | 0.9<br>0.7–1.2<br>(80/234)      | 1.3<br>1.1–1.6<br>(271/653)  | 1.5<br>1.2–2.0<br>(161/292)   | 1.3<br>0.9–1.7<br>(98/205)      |
| $>5$ –10 years                        | 1.5<br>1.2–1.8<br>(301/688)  | 1.9<br>1.4–2.5<br>(187/289)   | 1.3<br>0.9–1.8<br>(106/238)     | 1.4<br>1.1–1.8<br>(294/655)  | 1.8<br>1.3–3.4<br>(180/295)   | 1.2<br>0.9–1.7<br>(100/220)     |
| $>10$ –15 years                       | 1.4<br>1.1–1.9<br>(211/476)  | 1.7<br>1.2–2.3<br>(131/225)   | 1.3<br>0.9–2.0<br>(74/152)      | 1.4<br>1.1–1.9<br>(131/294)  | 2.0<br>1.3–2.9<br>(82/126)    | 1.2<br>0.8–1.9<br>(46/99)       |
| $>15$ –20 years                       | 1.6<br>1.1–2.2<br>(92/196)   | 2.2<br>1.5–3.4<br>(59/84)     | 1.0<br>0.6–1.7<br>(29/76)       | 1.7<br>1.1–2.5<br>(50/109)   | 2.6<br>1.5–4.4<br>(35/47)     | 0.9<br>0.4–1.8<br>(12/38)       |
| $>20$ –25 years                       | 2.1<br>1.3–3.2<br>(50/81)    | 2.3<br>1.3–4.1<br>(29/38)     | 2.2<br>1.1–4.6<br>(17/20)       | 1.4<br>0.5–3.8<br>(6/13)     | 1.4<br>0.3–5.9<br>(3/6)       | 1.9<br>0.4–10<br>(3/3)          |
| $>25$ years                           | 3.0<br>1.7–5.2<br>(29/33)    | 4.6<br>2.1–10<br>(19/13)      | 3.2<br>1.2–8.6<br>(10/9)        | –<br>(0/0)                   | –<br>(0/0)                    | –<br>(0/0)                      |

Table 6

Odds ratio (OR) and 95% confidence interval (CI) for glioma ( $n = 1380$ ) for cumulative use of wireless phones in quartiles based on use of wireless phones among controls in total. Numbers of exposed cases (Ca) and population-based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

| Quartile         | Analogue                    | Digital (2G)                 | Digital (UMTS, 3G)        | Mobile phone, total          | Cordless phone               | Digital type (2G, 3G, cordless) | Wireless phone               |
|------------------|-----------------------------|------------------------------|---------------------------|------------------------------|------------------------------|---------------------------------|------------------------------|
|                  | OR, CI (Ca/Co)              | OR, CI (Ca/Co)               | OR, CI (Ca/Co)            | OR, CI (Ca/Co)               | OR, CI (Ca/Co)               | OR, CI (Ca/Co)                  | OR, CI (Ca/Co)               |
| First quartile   | 1.2<br>0.9–1.6<br>(119/304) | 1.3<br>1.1–1.6<br>(328/885)  | 1.8<br>0.7–4.5<br>(16/47) | 1.3<br>1.05–1.5<br>(340/920) | 1.1<br>0.9–1.4<br>(174/478)  | 1.2<br>0.9–1.4<br>(214/618)     | 1.2<br>0.9–1.4<br>(223/641)  |
| Second quartile  | 1.8<br>1.3–2.5<br>(88/146)  | 1.3<br>1.01–1.7<br>(187/467) | 1.5<br>0.6–3.8<br>(17/54) | 1.3<br>1.02–1.6<br>(198/492) | 1.2<br>0.97–1.6<br>(203/534) | 1.3<br>1.1–1.6<br>(232/583)     | 1.3<br>1.04–1.6<br>(235/596) |
| Third quartile   | 1.8<br>1.2–2.8<br>(50/82)   | 1.5<br>1.1–1.9<br>(174/388)  | 3.0<br>1.2–7.5<br>(20/31) | 1.4<br>1.04–1.8<br>(179/416) | 1.6<br>1.3–2.1<br>(210/451)  | 1.4<br>1.1–1.7<br>(241/613)     | 1.4<br>1.1–1.7<br>(249/617)  |
| Fourth quartile  | 4.8<br>2.8–8.2<br>(42/26)   | 2.3<br>1.7–3.1<br>(195/274)  | 2.7<br>0.7–10<br>(5/9)    | 2.2<br>1.7–2.9<br>(228/320)  | 2.3<br>1.8–3.1<br>(165/261)  | 2.1<br>1.7–2.7<br>(350/579)     | 2.0<br>1.6–2.6<br>(367/618)  |
| <i>P</i> , trend | <0.0001                     | 0.0001                       | 0.37                      | <0.0001                      | <0.0001                      | <0.0001                         | <0.0001                      |

First quartile 1–122 h; second quartile 123–511 h; third quartile 512–1486 h, fourth quartile >1486 h

first use in the age groups 20–49 years and  $\geq 50$  years, being still statistically significant. These ORs also increased with ipsilateral use. Contralateral use of mobile or cordless phone use did not increase statistically significant the risk of glioma.

### 3.9. Using meningioma cases as referents

These case-control studies included all types of brain tumours reported to the Swedish cancer register, the majority of benign brain tumours being meningioma. In one analysis, meningioma cases ( $n = 1624$ ) were used as the reference

entity to glioma cases ( $n = 1379$ ). Table 9 shows a statistically significant increased risk for glioma associated with ipsilateral use of all phone types. Ipsilateral mobile phone use gave OR = 1.4, 95% CI = 1.1–1.8, and ipsilateral cordless phone OR = 1.4, 95% CI = 1.1–1.9.

### 3.10. Different types of glioma

Astrocytoma is the most common type of glioma. Regarding astrocytoma grade I–II (low grade;  $n = 221$ ) mobile phone use yielded OR = 1.5, 95% CI = 0.9–2.3,

Table 7

Odds ratio (OR) and 95% confidence interval (CI) for glioma per 100 h cumulative use in a multivariate analysis, and per year of latency adjusted for years of use of any mobile or cordless phone prior to the respective type. In all calculations adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis. Population based controls were used.

|                    | Per 100 h cumulative use |             | Per year of latency |             |
|--------------------|--------------------------|-------------|---------------------|-------------|
|                    | OR                       | 95% CI      | OR                  | 95% CI      |
| Analogue           | 1.025                    | 1.010–1.041 | 1.056               | 1.036–1.076 |
| Digital (2G)       | 1.009                    | 1.005–1.014 | 1.030               | 1.009–1.052 |
| Digital (UMTS, 3G) | 0.980                    | 0.944–1.017 | 1.127               | 0.955–1.329 |
| Cordless phone     | 1.011                    | 1.006–1.016 | 1.034               | 1.016–1.054 |

Table 8

Odds ratio (OR) and 95% confidence interval (CI) for glioma for age at first use of wireless phone. Numbers of exposed cases (Ca) and population-based controls (Co) are given. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

|                     | All      |     |          | Ipsilateral |     |         | Contralateral |     |         |
|---------------------|----------|-----|----------|-------------|-----|---------|---------------|-----|---------|
|                     | Ca/Co    | OR  | 95% CI   | Ca/Co       | OR  | 95% CI  | Ca/Co         | OR  | 95% CI  |
| Mobile phone, total | 945/2148 | 1.3 | 1.1–1.6  | 592/920     | 1.8 | 1.4–2.2 | 316/729       | 1.1 | 0.8–1.4 |
| <20 years old       | 69/93    | 1.8 | 1.2–2.8  | 39/38       | 2.3 | 1.3–4.2 | 22/28         | 1.9 | 0.9–3.7 |
| 20–49 years old     | 605/1337 | 1.3 | 1.1–1.6  | 384/573     | 1.8 | 1.4–2.3 | 198/447       | 1.1 | 0.8–1.5 |
| $\geq 50$ years old | 271/718  | 1.3 | 1.1–1.6  | 169/309     | 1.7 | 1.3–2.2 | 96/254        | 1.1 | 0.8–1.5 |
| Cordless phone      | 752/1724 | 1.4 | 1.1–1.7  | 461/766     | 1.7 | 1.3–2.1 | 259/565       | 1.2 | 0.9–1.6 |
| <20 years old       | 46/48    | 2.3 | 1.4–3.9  | 28/19       | 3.1 | 1.6–6.3 | 10/15         | 1.5 | 0.6–3.8 |
| 20–49 years old     | 436/1022 | 1.3 | 1.02–1.6 | 265/458     | 1.5 | 1.2–2.0 | 158/334       | 1.2 | 0.9–1.7 |
| $\geq 50$ years old | 270/654  | 1.4 | 1.2–1.8  | 168/289     | 1.8 | 1.4–2.3 | 91/216        | 1.2 | 0.9–1.7 |

Table 9

Odds ratio (OR) and 95% confidence interval (CI) for glioma ( $n = 1379$ ) and meningioma cases ( $n = 1624$ ) as the reference entity. Numbers of exposed cases (Ca) and controls (Co) are given. One subject with both a malignant brain tumour and meningioma was excluded from the analysis. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis.

|                     | All     |     |          | Ipsilateral |     |         | Contralateral |     |         |
|---------------------|---------|-----|----------|-------------|-----|---------|---------------|-----|---------|
|                     | Ca/Co   | OR  | 95% CI   | Ca/Co       | OR  | 95% CI  | Ca/Co         | OR  | 95% CI  |
| Analogue            | 299/221 | 1.3 | 0.98–1.8 | 190/106     | 1.7 | 1.2–2.5 | 98/75         | 1.2 | 0.8–2.0 |
| Digital (2G)        | 883/902 | 1.3 | 0.99–1.6 | 549/432     | 1.5 | 1.1–2.0 | 298/329       | 1.0 | 0.7–1.4 |
| Digital (UMTS, 3G)  | 58/47   | 2.8 | 1.2–6.7  | 35/26       | 3.3 | 1.2–8.8 | 21/17         | 1.8 | 0.6–5.2 |
| Mobile phone, total | 944/955 | 1.2 | 0.97–1.5 | 591/458     | 1.4 | 1.1–1.8 | 316/342       | 1.0 | 0.7–1.4 |
| Cordless phone      | 751/816 | 1.2 | 0.9–1.5  | 461/378     | 1.4 | 1.1–1.9 | 258/289       | 1.1 | 0.8–1.6 |

increasing to OR = 2.1, 95% CI = 0.8–5.8 in the >20 year latency group. Ipsilateral mobile phone use in that latency category gave OR = 3.0, 95% CI = 0.96–9.1; cordless phone use gave overall OR = 1.4, 95% CI = 0.9–2.3, and with latency >15–20 years OR = 1.6, 95% CI = 0.6–4.4, ipsilateral use OR = 3.2, 95% CI = 0.99–10. The calculations with longer latency time were based on small numbers of exposed cases (data not in Table).

Regarding astrocytoma grade III–IV (high grade;  $n = 857$ ), mobile phone use gave overall OR = 1.4, 95% CI = 1.1–1.8. The risk increased in the >20 year latency group to OR = 2.5, 95% CI = 1.6–3.8 and for ipsilateral use to OR = 3.3, 95% CI = 1.9–5.7. Cordless phone use gave OR = 1.5, 95% CI = 1.2–1.9. Ipsilateral use in the latency group >15–20 years gave OR = 2.5, 95% CI = 1.3–4.8. Only 4 cases had used the cordless phone >20 years, making these calculations less meaningful (data not in Table).

Wireless phone use gave for oligodendroglioma ( $n = 162$ ) OR = 1.6, 95% CI 0.998–2.5 overall, increasing to OR = 3.2, 95% CI = 1.2–8.3 in the >20 years latency group. For other types or mixed glioma ( $n = 140$ ), wireless phone use gave in total OR = 1.1, 95% CI = 0.7–1.8, increasing to OR = 2.7, 95% CI = 1.02–7.4 using >20 years latency (data not in Table).

### 3.11. Other tumour types than glioma

In total 118 cases had some other type of malignant brain tumour than glioma (including medulloblastoma, ependymoma, other malignant; Table 1). Mobile phone use in total gave OR = 1.4, 95% CI = 0.8–2.4, increasing to OR = 2.9, 95% CI = 0.9–9.6 in the >20 year latency group. The corresponding values for cordless phone use were OR = 1.3, 95% CI = 0.8–2.4 and OR = 2.8, 95% CI = 0.98–7.9, respectively. Several of the calculations were based on small numbers (data not in Table).

### 3.12. Unconditional versus conditional logistic regression analysis

We also used conditional logistic regression analysis to find if dissolving of the matching and including all controls in the study had an impact on the results. This gave OR = 1.3, 95% CI = 1.1–1.6 for mobile phone use, which

is the same as in the unconditional analysis. For cordless phone use, the result was OR = 1.5, 95% CI = 1.3–1.9, and for wireless phone use in total OR = 1.4, 95% CI = 1.2–1.7, i.e. slightly higher ORs than in the unconditional logistic regression analysis.

### 3.13. Restricted cubic spline plots

A restricted cubic spline plot (Fig. 1) shows the relationship between cumulative use of wireless phones and glioma, there being a linear trend of increasing risk up to 10,000 h of cumulative use (non-linearity,  $P = 0.08$ ). A linear relationship between latency of wireless phone use and the risk of glioma was detected (Fig. 2; non-linearity,  $P = 0.71$ ).

The results for latency and ipsilateral mobile phone use (Fig. 3) show that there was a higher OR with short latency, and after some decline was seen to give an increasing risk with longer latency (non-linearity,  $P = 0.01$ ). This finding is different from the result for contralateral mobile phone use, see Fig. 4 (non-linearity,  $P = 0.74$ ). The results were similar for cordless phone use, data not in figures (ipsilateral, non-linearity,  $P = 0.04$ , contralateral, non-linearity,  $P = 0.26$ ).

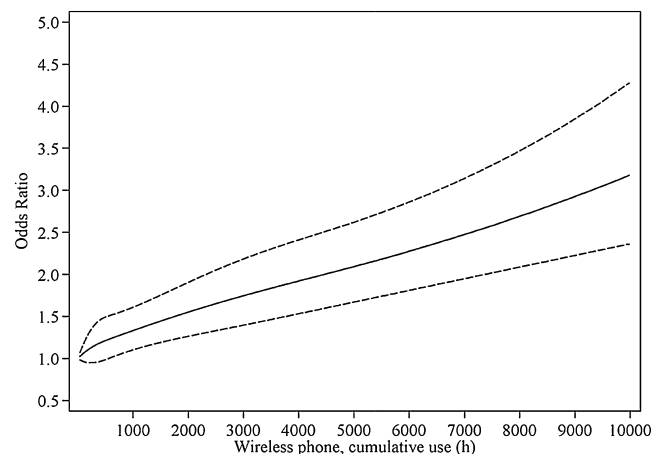


Fig. 1. Restricted cubic spline plot of the relationship between cumulative use of wireless phones and glioma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis. Population based controls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

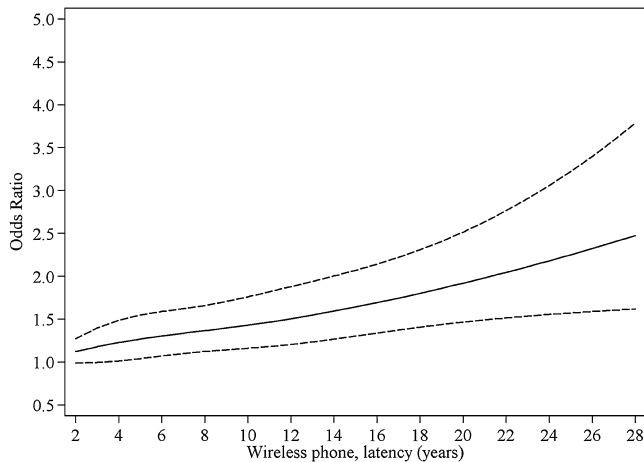


Fig. 2. Restricted cubic spline plot of the relationship between latency of wireless phones and glioma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis. Population based controls were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

## 4. Discussion

### 4.1. The main findings

Most of the types of malignant brain tumours were glioma ( $n = 1380$ , 92.1%). The most malignant variety, astrocytoma grade IV (glioblastoma multiforme) constituted 50.3% of the gliomas. In contrast to e.g., Interphone [16], we publish also results for different types of glioma. This study clearly shows an increased risk for glioma associated with use of both mobile and cordless phones, a risk that increased significantly with latency and cumulative use. The highest risk was in the longest latency group (>25 years), giving a statistically significant 3-fold increased risk. Overall a high risk was found for use of the third generation (3G; UMTS) mobile

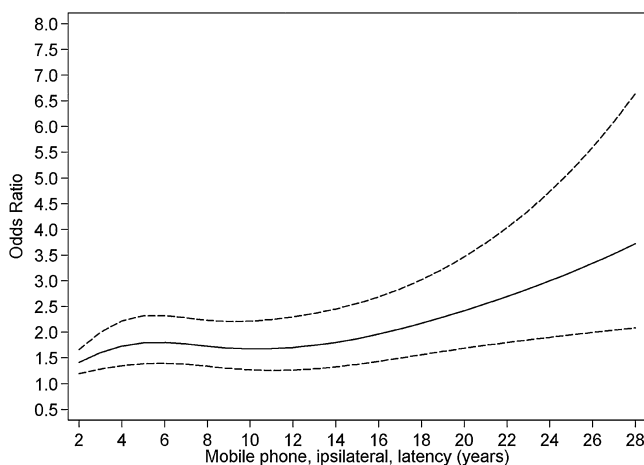


Fig. 3. Restricted cubic spline plot of the relationship between latency of ipsilateral mobile phone use and glioma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis. Population based controls were used.

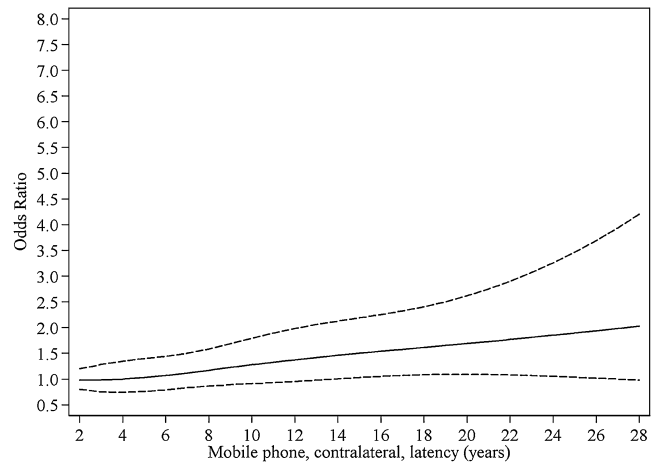


Fig. 4. Restricted cubic spline plot of the relationship between latency of contralateral mobile phone use and glioma. The solid line indicates the OR estimate and the broken lines represent the 95% CI. Adjustment was made for age at diagnosis, gender, SEI-code, and year for diagnosis. Population based controls were used.

phones, with OR = 4.1, 95% CI = 1.3–12 in the latency group >5–10 years. The risk for 3G use increased with 4.7% per 100 h cumulative use and with 15.7% per year of latency. Several calculations, however, were based on small numbers, and most of the subjects had previously used another mobile phone type. In a multivariate analysis, no statistically significant increased risk per 100 h cumulative use was found for 3G; this was also the case in the analysis of OR per year of latency with adjustment of previous use of other phone types.

As expected based on the distribution of RF-EMF on the brain, ipsilateral use of both mobile and cordless phones gave a statistically significant increased risk, whereas no statistically significant increased risk was found for contralateral use, which is in agreement with previous results (for discussion see [8,29]). There was a higher risk for glioma in the temporal or overlapping lobes, especially for glioma localised only in the temporal lobe. Based on dosimetry, these results are also expected, being similar to our previous findings [24,30].

Children and adolescents are more exposed to RF-EMF than adults due to thinner skull bone, higher conductivity in the brain tissue, and a smaller head. Also the developing brain is more vulnerable than in adults and it is still developing until about 20 years of age [31]. We analysed glioma risk in different age groups for first use of a wireless phone. Regarding both mobile and cordless phones OR was highest among subjects with first use before 20 years of age. The risk increased further for ipsilateral use to OR = 2.3, 95% CI = 1.3–4.2 for mobile phone use and to OR = 3.1, 95% CI = 1.6–6.3 for cordless phone use. These results are consistent with our previous findings [8,15,29,30].

We used restricted cubic spline plots to illustrate the relationship between both cumulative use and latency of wireless phones and glioma. There was a linear increase in risk up to 10,000 h cumulative use (non-linearity,  $P = 0.08$ ). Latency

also gave a linear increasing risk with data up to 28 years (non-linearity  $P=0.71$ ). For ipsilateral mobile phone use and latency, the curve was slightly different compared with total wireless phone use, with an increased risk for short latency (<10 years), which dropped off slightly before increasing again with longer latency >20 years (non-linearity  $P=0.01$ ). This finding differs from contralateral mobile phone use, compare Figs. 3 and 4. It should be noted that contralateral use was defined as less than 50% of the time. Similar results were found for cordless phone use. These results indicate an early effect in brain tumourigenicity (initiation) and a late effect (promotion), as discussed elsewhere [24].

#### 4.2. Strengths and limitations

Patients in this study, with histopathological verification of a malignant brain tumour, were reported to us from the cancer registries in Sweden; for 1997–2003, cases were ascertained from central Sweden, whereas for 2007–2009 the whole country was included. Controls were selected from the same geographical area as the cases, with matching made on year of diagnosis, gender, and age, making the controls comparable with the cases. All the controls could be included in the unconditional logistic regression analysis because adjustment was made for year of diagnosis, gender, age, and SEI-code. In the laterality analysis, the matched control was assigned the same side of localisation as the tumour for the respective case.

In one of the analyses, we used conditional logistic regression, and thus the overall results were similar or gave slightly higher ORs than in the unconditional analysis using the whole set of controls. Thus, our analysis gave rather conservative risk estimates. Using the whole material allowed us to make several subgroup analyses that would otherwise have been hampered by small numbers of exposed subjects.

One strength of our study was the high percentage of participating cases and controls, 89% and 87%, respectively, making it unlikely that selection bias influenced the results. It might be argued that excluding deceased cases could bias the results, however in a special study that included the deceased cases for 1997–2003, using deceased controls, we concluded that mobile phone use was a risk factor for glioma [25]. For both study groups, the next of kin answered the questionnaire on the use of wireless phones. Thus, the inclusion of only living subjects in the present study would not have biased the results.

Recall bias might have been an issue, such that cases would have overestimated their use of wireless phones. To address this point, we used meningioma cases from the same study as the reference entity in one analysis, which showed an increased risk of glioma with wireless phone use. Thus it is unlikely that our present results using population-based controls are explained by recall bias.

Observational bias might have been introduced by the supplementary phone interviews. However, the identity of the subjects either as a case or a control was not disclosed to

the interviewer. A structured protocol was also used and the interviewer had to follow that procedure strictly during the interviews. Also the different results according to tumour type in this study do not support observational bias, since even had an interviewer identified a subject being a case, no information was available regarding the histopathology of the brain tumour.

All data processing before statistical analysis was done without information about case/control status of the subjects. Histopathological classification of the tumour was made without knowledge of exposure. Tumour pathology was coded in a separate data file that was not disclosed before statistical analysis.

#### 4.3. Biological considerations

Several findings, discussed to some extent above, give the findings in this study their biological relevance. We also found highest risk in the most exposed part of the brain, i.e. ipsilateral exposure and the temporal lobe.

As might also be anticipated, OR increased with cumulative use and latency. Regarding the latter, ipsilateral exposure indicated an early effect in glioma development, which is an increased risk with long latency. However, we also found an increased risk with short latency, indicating a late effect in tumour development. Thus, as discussed elsewhere [24], these results could be compatible with both tumour initiation and promotion.

Of certain interest is the higher risk we observed for 3G mobile phone use compared with other types. However, this observation was based on short latency and rather low numbers of exposed subjects. Contrary to 2G GSM, 3G universal global telecommunications system (UMTS) mobile phones emit wide-band microwave (MW) signals. Hypothetically, UMTS MWs may result in higher biological effects compared to GSM signal because of eventual “effective” frequencies within the wideband [32,33]. To our knowledge, there are only two mechanistic studies, which compare effects of 2G and 3G signals using the same experimental approach under well-defined conditions of exposure [32,34]. UMTS MWs affected chromatin and inhibit formation of DNA double-strand breaks (DSB) co-localizing 53BP1/gamma-H2AX DNA repair foci in human lymphocytes from hypersensitive and healthy persons [32]. The data were in line with the hypothesis that the type of signal, UMTS MWs, may have higher biological efficiency and possibly larger health risk effects compared to GSM radiation emissions. The effects of UMTS MWs and GSM-915 MHz MWs on the formation of the DNA repair foci, were statistically different for hypersensitive but not for control subjects [32].

Chronic exposure to GSM and UMTS signals resulted in significant inhibition of DSB repair in human stem cells [34]. Statistical analysis revealed that UMTS exposure affected human stem cells more strongly than did the GSM exposure [34]. Inhibitory effects of MW exposure on DSB repair in stem cells may result in formation of chromosomal

aberrations and therefore origination of cancer. Alternatively, MW exposures may induce a stress response. Both possible interpretations provided a mechanistic link to increased cancer risk because stem cells are considered as most relevant targets for origination of tumours of different types including glioma [34]. One interesting gene is the *p53* protein. It is a transcription factor that plays a vital role in regulating cell growth, DNA repair and apoptosis, and *p53* mutations are involved in disease progression. In a recent study it was found that use of mobile phones for  $\geq 3$  hours a day was associated with increased risk for the mutant type of *p53* gene expression in the peripheral zone of astrocytoma grade IV. Furthermore, this mutation increase was statistically significant correlated with shorter overall survival time [35]. The study was rather small ( $n = 63$ ) and no data on latency of mobile phone use was given.

Ionizing radiation and heredity are known risk factors for glioma, but these were independent risk factors with no interaction with wireless phones [36]. Thus, it was unnecessary to make adjustment for these factors in the statistical analysis.

In analysis of survival of glioma cases in our previous studies [13,15,25], we found a decreased survival of cases with glioblastoma multiforme and long-term use of wireless phones [37,38]; this indicates a complex biological effect from RF-EMF exposure and strengthens a causal association between glioma and the use of wireless phones.

We have already shown a higher risk for glioma among subjects with first use of a mobile or cordless phone before the age of 20 years [8,15,29,30], which was also the result found in the present study. In particular, the near field exposure to the brain from a handset is worrying since the exposure is higher in children than adults due to the thinner bone, smaller head and higher conductivity of microwaves in the brain. Moreover, the developing brain is discussed to be more sensitive to toxins than that of the adult [39].

In short, these findings on biological relevance are consistent with wireless phones causing glioma. The Hill viewpoints on association and causation are useful in this context. As published elsewhere [20], adopting the Hill criteria agrees with the conclusion that RF-EMF emissions from wireless phones cause glioma. Laboratory studies also support this notion. These findings have been discussed elsewhere [24] and have also been reviewed by IARC [10,12], and therefore will not be commented on any further.

#### 4.4. Other human studies

We previously reviewed this topic [8] and will therefore give only a short summary. In Interphone, a statistically significant increased risk for glioma was seen in the group 2–4 years for regular use, with 1–1.9 years use as reference category, OR = 1.68, 95% CI = 1.16–2.41 (see Appendix 2) [16]. The highest OR was in the 10+ years category for regular use, OR = 2.18, 95% CI = 1.43–3.31. Results have not been presented according to type of mobile phone used. Overall, cumulative use  $\geq 1640$  h in the shortest latency group of 1–4

years before reference date was associated with increased risk, OR = 3.77, 95% CI = 1.25–11.4.

In Interphone, cumulative call-time of mobile phones  $\geq 1640$  h resulted in OR = 1.87, 95% CI = 1.09–3.22 for glioma in the temporal lobe, and for ipsilateral mobile phone OR = 1.96, 95% CI = 1.22–3.16 [16]. Likewise, in the present study, the OR was higher for ipsilateral use of mobile or cordless phones, and for glioma in the temporal and overlapping lobes. Re-analysis of our data using the same criteria for inclusion and exposure gave similar results as in Interphone [40]. Also in the current pooled analysis excluding cordless phone use (regarded as no exposure to RF-EMF) and limiting the age group to 30–59 years gave conservative risk estimates. Thus mobile phone use in total gave OR = 1.2, 95% CI = 0.95–1.5. No statistically significant increased risk was found in the different latency groups except for time since first use  $>25$  years (latency). That result was based on use of analogue phones ( $n = 18$  cases, seven controls) and gave OR = 6.7, 95% CI = 2.6–17 using the Interphone criteria (data not in Table). These results indicate that several methodological limitations in Interphone, such as excluding use of cordless phones and the limited age group, hampered the possibility to find a true risk increase. Of course results on cordless phone use and the use of a reference category of no wireless phone use would have been desirable in Interphone.

The highest incidence of astrocytoma WHO grade IV (glioblastoma multiforme) is found in the age group 45 to 75 years with mean age 61 years and 80% older than 50 years [8]. Limiting upper 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 and a reasonable latency time. Excluding the youngest age group, as in Interphone, makes also an evaluation of young users more difficult.

There are few other current studies. In the French CERE-NAT study, regular use of mobile phone gave for brain tumour OR = 1.24, 95% CI = 0.86–1.77 [41]. However, a statistically significant association was observed for gliomas in the heaviest users when considering a life-long cumulative duration of calls  $\geq 896$  h yielding OR = 2.89, 95% CI = 1.41–5.93. Risks were higher for temporal tumours, occupational or urban mobile phone use.

In a record linkage study from Denmark, mobile phone subscribers from January 1, 1982, until December 31, 1995, were identified from the computerised files of the 2 Danish operating companies, TeleDenmark Mobil and Sonofon, which also partly funded the study [9]. It has produced four articles that we thoroughly reviewed [11]. We concluded that its many limitations – embedded in the study design from the very beginning and mainly related to poor exposure assessment – obscure the findings of the four reports to such an extent that, at best, render them uninformative. This Danish cohort study was included in the IARC evaluation of RF-EMF, but the conclusion was that the “phone provider, as a

surrogate for mobile phone use, could have resulted in considerable misclassification in exposure assessment” [10]. Thus, this study is uninformative as to cancer risks from mobile phone use.

There are few other studies on brain tumour risk for children from use of wireless phones. A multi-centre case-control study was conducted in Denmark, Sweden, Norway, and Switzerland, CEFALO [42]. It included children and adolescents aged 7–19, and has been discussed elsewhere in detail since serious methodological problems were identified in the study design and interpretation of the results [43].

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 slightly with cumulative duration of subscriptions and duration of calls [42]. No data for long-term use were given, and the longest latency period was 5 years. Interestingly, support for a true association was found in the results based on operator-recorded use for 62 cases and 101 controls, which for the time since first subscription being >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 this was covered only in the first 3 years of use, but no explanation was given for this most peculiar definition.

Evidence relating to trends in the incidence of glioma is not discussed here, since it has been reviewed in other publications [8,24]. A recent up-date of the Danish Cancer Register showed an increasing incidence of brain tumours during 2003–2012, 41.2% among men and 46.1% in women (<http://www.ssi.dk/Aktuelt/Nyheder/2013/~media/Indhold/DK%20-%20dansk/Sundhedsdata%20og%20it/NSF/Registre/Cancerregisteret/Cancerregisteret%202012.ashx>).

#### 4.5. Conclusion

We previously analysed the evidence on glioma associated with the use of wireless phones using the Hill criteria [20]. We concluded that glioma and also acoustic neuroma are caused by RF-EMF emissions from wireless phones, and thus regarded as carcinogenic, under Group 1 according to the IARC classification, indicating that current guidelines for exposure should be urgently revised. This pooled analysis gives further support to that conclusion regarding glioma.

#### Authors' contributions

Lennart Hardell was the principal investigator and responsible for drafting of the manuscript. Michael Carlberg made all statistical calculations. Both authors contributed to the writing of this article and have read and approved the final version. No conflicts of interest exist.

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