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# Case–control study of the association between the use of cellular and cordless telephones and malignant brain tumors diagnosed during 2000–2003 ☆

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**Abstract**

We performed a case–control study on the use of cellular and cordless telephones and the risk for brain tumors diagnosed during 2000–2003. We report the results for malignant brain tumors with data from 317 cases (88%) and 692 controls (84%). The use of analog cellular phones yielded odds ratio (OR) of 2.6 and a 95% confidence interval (CI) of 1.5–4.3, increasing to OR = 3.5 and 95% CI = 2.0–6.4 with a >10-year latency period. Regarding digital cellular telephones, the corresponding results were OR = 1.9, 95% CI = 1.3–2.7 and OR = 3.6, 95% CI = 1.7–7.5, respectively. Cordless telephones yielded OR = 2.1, 95% CI = 1.4–3.0, and with a >10-year latency period, OR = 2.9, 95% CI = 1.6–5.2. The OR increased with the cumulative number of hours of use and was highest for high-grade astrocytoma. A somewhat increased risk was also found for low-grade astrocytoma and other types of malignant brain tumors, although not significantly so. In multivariate analysis, all three phone types studied showed an increased risk.
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## 1. Introduction

In previous epidemiological studies we found an association between the use of cellular telephones and brain tumors (Hardell et al., 1999, 2001, 2002a, b, 2003a, b). However, for salivary gland tumors no association was found, although the parotid gland is located in an area with high exposure to microwaves from cellular telephones compared to other anatomical sites (Hardell et al., 2004). These and other results on this topic have been reviewed recently elsewhere (Hansson Mild et al., 2003; Kundi, 2004; Kundi et al., 2004) and are not discussed here further.

In epidemiological studies the assessment of microwave exposure is usually based on the type of phone [Nordic Mobile Telephone System (NMT), Global System for Mobile Communication (GSM), and cordless] and the years and cumulative numbers of hours of use. There is variation in the specific absorption rate (SAR) of the different types of cellular telephones. However, this information is not easily available, since mostly the subjects cannot remember the brand names of the cellular phones used over time. Moreover, information from the manufacturers on the SAR is usually lacking.

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During cellular phone calls, radio frequency (RF) signals in the range of 400–2000 MHz are used. In Sweden, the analog NMT system was introduced in 1981 and operated at 450 MHz, often in a car with a fixed external antenna, but from 1984 the first portable analog phones were available. The NMT 900-MHz system operated in Sweden between 1986 and 2000. The digital GSM system started in 1991 and has been the most common phone since the end of the 1990s in Sweden. Moreover, desktop cordless telephones have been used in Sweden since 1988. At first, the analog system in the range of 800–900 MHz RF was used, but now usually digital cordless telephones that operate at 1900 MHz are used.

The aim of the present study was to further investigate an association between the use of cellular and cordless telephones and brain tumors by extending our previous study with further years of patient accrual. We used a longer follow-up period of users, especially of digital cellular telephones. We used the same study method, including the questionnaire, as in our previous study. The results for the use of cellular and cordless telephones and their risk of malignant brain tumors are presented here. Results for benign tumors will be presented separately. The ethics committees at our institutions approved the study.

## 2. Materials and methods

Cases were recruited during the period July 1, 2000–December 31, 2003. There was no overlap with cases from our previous studies on this topic. Both men and women aged 20–80 years at the time of diagnosis, as defined according to the date of the histopathology report, were included. They were inhabitants of the Uppsala/Örebro and Linköping medical regions of Sweden. All had a histopathological diagnosis that had been reported to the regional cancer registries in Uppsala and Linköping. These registries sent information to our study group as soon as a new case was reported. Permission to include the patient in the study was asked of the treating physician. Only living patients were included.

In total 1168 cases were reported. The following cases were excluded since they did not meet the inclusion criteria: 205 were deceased (187 malignant), 56 had brain metastasis or localization other than the brain, 15 were not diagnosed within the dates of inclusion, 1 had missing histopathology, 46 were refused by the treating physician, 23 were not capable of participating for medical reasons, and 2 were not included due to other language. Thus, the final sample consisted of 820 cases in total, 359 of these having a malignant brain tumor, as will be reported here. One of these 359 cases had also a benign brain tumor.

Control subjects were identified from the national population registry covering the whole population. The controls were aged 20–80 years and lived in the same geographical area as the cases, the Uppsala/Örebro and Linköping medical regions. They were matched on age and selected at random in 5-year age groups according to the number of cases in the different age groups. One control was matched to each finally included case. Each study subject was given a unique identification number that did not reveal whether he or she was a case or a control. All of the controls in the study were included in the analysis.

### 2.1. Assessment of exposure

Exposures to cellular and cordless phones were assessed by a questionnaire sent by mail to all study subjects. It also included exposure to certain agents and lifetime work history, with which a socioeconomic index (SEI) was assessed. The SEI code was based on the current or last occupation reported in the questionnaire. If the study subject did not return a completed questionnaire, two reminders were sent, if necessary. The answers were supplemented over the telephone by a trained interviewer using a written protocol that prevented the disclosure of whether the respondent was a case or a control. All cases and controls were also interviewed over the telephone to verify exposures and get additional detailed information.

The mean numbers of daily calls and minutes were used to calculate the cumulative use in hours from the first year of use up to the year before diagnosis. This way the same year, i.e., year of diagnosis, was used for the matched control and for the corresponding case. Those that started their use of a mobile or cordless phone within 1 year prior to diagnosis were regarded as unexposed.

Use of a cellular telephone in a car with a fixed external antenna was disregarded. Similarly, the use of a hands-free device with an earpiece was excluded in the calculation of the total number of hours. We also assessed information on the ear most frequently used during calls with cellular and cordless telephones over the years or whether both ears were used equally. It was important to obtain the use of which ear for the entire time since some subjects might have changed their habit, e.g., due to the brain tumor.

Since it was important to differentiate between analog and digital cellular telephones, we checked the first part of the phone number (prefix). Thus, all analog phone numbers started with 010 and digital with 07. If the first year that the subject reported for the use of a cellular or cordless phone was apparently incorrect, i.e., it was before the respective telephone was on the market, this was corrected during the interviews and coding of exposure.

The histopathology was obtained from the cancer registry and, if missing, from pathology departments; i.e., all histopathology reports are sent to the cancer registries. Information on tumor localization, based on the clinical examinations, was also for many cases available in the Cancer Registry report. In order to get the correct diagnosis and tumor localization, copies of reports of neuroradiology investigations were requested from radiology units at different hospitals, if necessary. This was accomplished after informed consent was received from the cases. We had no missing data for histopathology or tumor localization. All coding of the anatomical area of the tumor was completed without the knowledge of whether the subject was exposed to cellular or cordless phones. The use of cellular and cordless phones was coded by two independent persons and yielded the same results in the statistical calculations.

### 2.2. Statistical methods

Unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) (Stata/SE 8.2 for Windows; StataCorp, College Station, TX, USA). This way incomplete pairs could also be included in the analysis. The material was divided into two groups, exposed and unexposed. The exposed cases and controls were further divided according to telephone type: analog, digital, and cordless. Note that a person may have been using more than one type of telephone. The unexposed group consisted of cases and controls without exposure to cellular or cordless telephones. Adjustments were made for sex, age, SEI code, and year of diagnosis. The same year as for the case was used for the corresponding control. In that way we could adjust for any difference in year of diagnosis for cases and controls in the different analysis. Age was used as continuous variable in the analysis. The latency, or tumor induction, period was analyzed using three time periods, 1–5 years, >5–10 years, and >10 years since the first use of a cellular or cordless telephone until tumor diagnosis. In the dose–response calculations, the median number of cumulative use in hours among controls was used as the cutoff. Note that the overall results for all three of the latency groups were calculated in one analysis for each telephone type, whereas the dose–response was analyzed separately for each category.

## 3. Results

Of the included 359 cases with a malignant brain tumor, 317 (88%; $n = 189$ men, 128 women) participated. The entire study encompassed 820 controls and of them 692 (84%) ($n = 292$ men, 400 women) answered the questionnaire. The mean age was 54 years for cases and 55 years for controls.

No use of cellular or cordless telephones was reported by 63 cases and 233 controls. In Table 1 the overall results are presented for the use of cellular and cordless telephones. The use of analog telephones yielded OR = 2.6, 95% CI = 1.5–4.3, increasing to OR = 3.5, 95% CI = 2.0–6.4, when a >10-year latency period was applied. The risk increased further with longer latency periods; for >15 years, OR = 6.1, 95% CI = 2.5–15 (22 cases, 12 controls). Digital cellular telephones yielded OR = 1.9, 95% CI = 1.3–2.7, and with a >10-year latency period, OR = 3.6, 95% CI = 1.7–7.5. The use of cordless telephones also gave a significantly increased risk, the highest being with a >10-year latency time at OR = 2.9, 95% CI = 1.6–5.2. In total, the OR increased for all phone types with the cumulative number of hours using the median number of hours among the controls as the cutoff.

Regarding different types of malignant brain tumors, the highest risk was found for high-grade astrocytoma. With a >10-year latency period, analog phones yielded OR = 4.7, 95% CI = 2.4–9.2, digital cellular phones OR = 4.5, 95% CI = 2.0–10, and cordless phones OR = 3.7, 95% CI = 1.8–7.2. No significant associations were found for low-grade astrocytoma. Regarding the use of digital cellular phones, there was a significant trend for the latency period for astrocytoma ($P = 0.04$) and high-grade astrocytoma ($P = 0.01$).

In Table 2, the OR and 95% CI are presented for different tumor localizations. An increased risk was found for tumors located in the temporal, frontal, or other parts of the brain. There was no clear pattern of increased risk only in the temporal area.

In Table 3, the results for a >1-year latency period are presented for the anatomical tumor area in relation to which ear had been used primarily during phone calls or whether both ears had been used equally. In general, the highest risk was found for ipsilateral use, but an increased risk was also found for contralateral phone use. Some of the calculations were based on low numbers, e.g., for low-grade astrocytoma.

Table 4 presents results for multivariate analysis. For all malignant brain tumors, both analog and cordless phones were significant risk factors. The analysis of high-grade astrocytoma yielded a significantly increased risk for analog and digital cellular telephones with a >10-year latency period. Also, cordless phones increased the risk, although not significantly.

We calculated also the OR and CI for different telephone types used solely or in combination. For this analysis, a >1-year latency period was used, as presented in Table 5. Few subjects had used analog phones only. For digital cellular phones only, the OR was calculated as 1.8, 95% CI = 1.1–2.9, for all

Table 1
Number of exposed cases (Ca) with malignant brain tumor and controls (Co), odds ratios (OR), and 95% confidence intervals (CI) for the use of cellular or cordless telephones

| | 1–5-year latency | | >5–10-year latency | | >10-year latency | | Total, >1-year latency | |
|---|---|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Malignant* ($n = 317$, 63 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 20/36 | 1.8<br>0.9–3.5 | 48/40 | 3.5<br>2.0–6.4 | 68/79 | 2.6<br>1.5–4.3 |
| ⩽80 h | 0/3 | — | 9/24 | 1.1<br>0.5–2.7 | 8/13 | 2.2<br>0.8–5.7 | 17/40 | 1.4<br>0.7–2.8 |
| >80 h | 0/0 | — | 11/12 | 2.6<br>0.99–7.0 | 40/27 | 4.9<br>2.5–9.7 | 51/39 | 4.0<br>2.2–7.3 |
| Digital | 100/214 | 1.6<br>1.1–2.4 | 79/111 | 2.2<br>1.4–3.4 | 19/18 | 3.6<br>1.7–7.5 | 198/343 | 1.9<br>1.3–2.7 |
| ⩽64 h | 55/139 | 1.5<br>0.9–2.3 | 24/44 | 1.9<br>1.03–3.4 | 0/0 | — | 79/183 | 1.6<br>1.1–2.4 |
| >64 h | 45/75 | 2.1<br>1.2–3.6 | 55/67 | 2.5<br>1.4–4.3 | 19/18 | 3.6<br>1.7–7.5 | 119/160 | 2.4<br>1.6–3.7 |
| Cordless | 83/170 | 1.8<br>1.2–2.8 | 58/100 | 2.1<br>1.3–3.4 | 30/35 | 2.9<br>1.6–5.2 | 171/305 | 2.1<br>1.4–3.0 |
| ⩽243 h | 59/110 | 1.9<br>1.2–3.0 | 17/37 | 1.7<br>0.9–3.3 | 5/12 | 1.3<br>0.4–4.1 | 81/159 | 1.8<br>1.2–2.8 |
| >243 h | 24/60 | 1.5<br>0.8–2.8 | 41/63 | 2.6<br>1.5–4.5 | 25/23 | 4.1<br>2.1–8.3 | 90/146 | 2.4<br>1.5–3.6 |
| *Astrocytoma, total* ($n = 248$, 50 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 17/36 | 2.1<br>1.002–4.4 | 40/40 | 3.7<br>2.0–7.0 | 57/79 | 2.9<br>1.6–5.0 |
| ⩽80 h | 0/3 | — | 8/24 | 1.3<br>0.5–3.4 | 6/13 | 2.2<br>0.8–6.5 | 14/40 | 1.6<br>0.8–3.3 |
| >80 h | 0/0 | — | 9/12 | 2.7<br>0.97–7.7 | 34/27 | 5.4<br>2.6–11 | 43/39 | 4.3<br>2.3–8.2 |
| Digital | 71/214 | 1.6<br>0.99–2.5 | 66/111 | 2.4<br>1.4–3.8 | 16/18 | 3.6<br>1.6–7.8 | 153/343 | 1.9<br>1.3–2.9 |
| ⩽64 h | 40/139 | 1.5<br>0.9–2.4 | 19/44 | 2.0<br>1.03–3.8 | 0/0 | — | 59/183 | 1.6<br>1.01–2.5 |
| >64 h | 31/75 | 2.0<br>1.1–3.6 | 47/67 | 2.7<br>1.5–5.0 | 16/18 | 3.6<br>1.6–7.8 | 94/160 | 2.4<br>1.5–3.9 |
| Cordless | 63/170 | 1.9<br>1.2–3.0 | 45/100 | 2.1<br>1.3–3.4 | 25/35 | 3.0<br>1.6–5.6 | 133/305 | 2.1<br>1.4–3.1 |
| ⩽243 h | 45/110 | 1.9<br>1.2–3.2 | 14/37 | 1.8<br>0.9–3.6 | 5/12 | 1.7<br>0.5–5.5 | 64/159 | 1.9<br>1.2–3.0 |
| >243 h | 18/60 | 1.5<br>0.8–3.1 | 31/63 | 2.6<br>1.4–4.9 | 20/23 | 4.1<br>1.9–8.8 | 69/146 | 2.3<br>1.5–3.8 |
| *Astrocytoma, high grade* ($n = 204$, 43 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 14/36 | 2.5<br>1.1–5.5 | 38/40 | 4.7<br>2.4–9.2 | 52/79 | 3.6<br>1.9–6.5 |
| ⩽80 h | 0/3 | — | 6/24 | 1.4<br>0.5–4.0 | 6/13 | 3.2<br>1.05–9.6 | 12/40 | 1.9<br>0.8–4.1 |
| >80 h | 0/0 | — | 8/12 | 3.9<br>1.3–12 | 32/27 | 7.4<br>3.4–16 | 40/39 | 5.7<br>2.8–11 |
| Digital | 56/214 | 1.6<br>1.01–2.7 | 58/111 | 2.8<br>1.7–4.7 | 15/18 | 4.5<br>2.0–10 | 129/343 | 2.2<br>1.4–3.3 |
| ⩽64 h | 34/139 | 1.7<br>0.96–2.9 | 18/44 | 2.4<br>1.2–4.8 | 0/0 | — | 52/183 | 1.8<br>1.1–2.9 |
| >64 h | 22/75 | 2.1<br>1.05–4.1 | 40/67 | 3.3<br>1.7–6.4 | 15/18 | 4.5<br>2.0–10 | 77/160 | 2.7<br>1.6–4.5 |
| Cordless | 47/170 | 2.0<br>1.2–3.4 | 37/100 | 2.4<br>1.4–4.2 | 22/35 | 3.7<br>1.8–7.2 | 106/305 | 2.4<br>1.5–3.7 |
| ⩽243 h | 33/110 | 2.0<br>1.1–3.4 | 12/37 | 2.2<br>0.98–4.8 | 5/12 | 3.0<br>0.9–10 | 50/159 | 2.1<br>1.3–3.4 |

Table 1 (*continued*)

| | 1–5-year latency | | >5–10-year latency | | >10-year latency | | Total, >1-year latency | |
|---|---|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| >243 h | 14/60 | 1.8<br>0.8–3.8 | 25/63 | 3.5<br>1.7–6.9 | 17/23 | 5.3<br>2.3–12 | 56/146 | 2.8<br>1.7–4.8 |
| *Astrocytoma, low grade* (*n* = 44, 7 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 3/36 | 1.4<br>0.3–7.3 | 2/40 | 1.2<br>0.2–7.7 | 5/79 | 1.2<br>0.3–4.9 |
| ⩽80 h | 0/3 | — | 2/24 | 1.8<br>0.3–13 | 0/13 | — | 2/40 | 1.0<br>0.2–6.1 |
| >80 h | 0/0 | — | 1/12 | 1.3<br>0.1–15 | 2/27 | 1.8<br>0.3–12 | 3/39 | 1.4<br>0.3–7.2 |
| Digital | 15/214 | 1.4<br>0.5–4.1 | 8/111 | 1.3<br>0.4–4.5 | 1/18 | 1.5<br>0.1–15 | 24/343 | 1.4<br>0.5–3.8 |
| ⩽64 h | 6/139 | 1.1<br>0.3–3.9 | 1/44 | 0.4<br>0.04–4.6 | 0/0 | — | 7/183 | 0.9<br>0.3–3.2 |
| >64 h | 9/75 | 2.3<br>0.7–7.9 | 7/67 | 1.1<br>0.3–4.6 | 1/18 | 1.5<br>0.1–15.0 | 17/160 | 1.8<br>0.6–5.5 |
| Cordless | 16/170 | 1.5<br>0.5–4.2 | 8/100 | 1.3<br>0.4–4.1 | 3/35 | 1.3<br>0.3–5.9 | 27/305 | 1.4<br>0.5–3.7 |
| ⩽243 h | 12/110 | 2.4<br>0.8–7.2 | 2/37 | 1.9<br>0.3–11 | 0/12 | — | 14/159 | 1.6<br>0.6–4.5 |
| >243 h | 4/60 | 1.1<br>0.3–4.7 | 6/63 | 1.3<br>0.3–5.1 | 3/23 | 2.4<br>0.4–15 | 13/146 | 1.2<br>0.4–3.6 |
| *Other malignant* (*n* = 69, 13 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 3/36 | 0.8<br>0.2–3.6 | 8/40 | 3.1<br>0.9–10 | 11/79 | 1.6<br>0.6–4.4 |
| ⩽80 h | 0/3 | — | 1/24 | 0.5<br>0.1–4.1 | 2/13 | 2.1<br>0.3–13 | 3/40 | 0.9<br>0.2–3.7 |
| >80 h | 0/0 | — | 2/12 | 2.4<br>0.3–17 | 6/27 | 3.3<br>0.9–12 | 8/39 | 2.5<br>0.8–8.2 |
| Digital | 29/214 | 1.9<br>0.9–4.0 | 13/111 | 1.8<br>0.7–4.3 | 3/18 | 4.2<br>0.98–18 | 45/343 | 1.9<br>0.9–3.9 |
| ⩽64 h | 15/139 | 1.7<br>0.7–4.0 | 5/44 | 1.8<br>0.6–6.0 | 0/0 | — | 20/183 | 1.7<br>0.8–3.8 |
| >64 h | 14/75 | 2.6<br>1.03–6.7 | 8/67 | 1.5<br>0.5–4.8 | 3/18 | 4.2<br>0.98–18 | 25/160 | 2.2<br>0.96–4.9 |
| Cordless | 20/170 | 1.9<br>0.8–4.1 | 13/100 | 2.3<br>0.9–5.4 | 5/35 | 2.4<br>0.8–7.8 | 38/305 | 2.1<br>0.99–4.2 |
| ⩽243 h | 14/110 | 2.0<br>0.9–4.8 | 3/37 | 1.3<br>0.3–5.3 | 0/12 | — | 17/159 | 1.8<br>0.8–4.0 |
| >243 h | 6/60 | 1.4<br>0.4–4.4 | 10/63 | 2.2<br>0.8–6.2 | 5/23 | 4.4<br>1.2–16 | 21/146 | 2.4<br>1.1–5.4 |

Unconditional logistic regression analysis was adjusted for age, sex, SEI, and the year of diagnosis. In the dose–response calculations the median number of cumulative use in hours among controls in the total material was used as the cutoff.

malignant brain tumors, increasing to OR = 2.0, 95% CI = 1.1–3.4 for high-grade astrocytoma. Also, cordless phones only yielded a significantly increased risk for all malignant tumors, with OR = 1.9, 95% CI = 1.1–3.1. A higher OR was calculated for combinations of phones. Thus, the use of analog and digital cellular telephones and cordless phones yielded OR = 3.5, 95% CI = 1.8–6.6, for all malignant brain tumors and for high-grade astrocytoma yielded OR = 5.1, 95% CI = 2.4–11.

## 4. Discussion

We have in two previous studies found an increased risk for brain tumors associated with the use of cellular telephones (Hardell et al., 1999, 2001, 2002a, b, 2003a, b). The risk was highest on the same side of the brain as the cellular phone had been used and increased with the tumor induction period, which is of biological relevance. Regarding malignant brain tumors with ipsilateral localization, significantly increased risk was found for

Table 2
Number of exposed cases (Ca) with malignant brain tumor and controls (Co), odds ratios (OR), and 95% confidence intervals (CI) for the use of cellular or cordless telephones for different tumor localizations

| | 1–5-year latency | | >5–10-year latency | | >10-year latency | | Total, >1-year latency | |
|---|---|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Temporal* ($n = 97$, 20 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 7/36 | 1.7<br>0.6–4.9 | 18/40 | 3.2<br>1.3–7.7 | 25/79 | 2.4<br>1.1–5.4 |
| Digital | 30/214 | 1.4<br>0.7–2.8 | 28/111 | 2.2<br>1.1–4.4 | 5/18 | 2.6<br>0.8–8.2 | 63/343 | 1.7<br>0.95–3.2 |
| Cordless | 25/170 | 1.7<br>0.8–3.4 | 16/100 | 1.6<br>0.8–3.5 | 13/35 | 3.1<br>1.3–7.2 | 54/305 | 1.9<br>1.02–3.5 |
| *Frontal* ($n = 106$, 21 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 8/36 | 2.2<br>0.8–5.8 | 18/40 | 4.3<br>1.8–10 | 26/79 | 3.1<br>1.5–6.6 |
| Digital | 34/214 | 1.7<br>0.9–3.2 | 27/111 | 2.2<br>1.1–4.3 | 6/18 | 3.1<br>1.04–9.3 | 67/343 | 1.9<br>1.1–3.5 |
| Cordless | 29/170 | 2.0<br>1.03–3.8 | 20/100 | 2.3<br>1.1–4.6 | 8/35 | 2.3<br>0.9–6.0 | 57/305 | 2.1<br>1.2–3.8 |
| *Other parts* ($n = 114$, 22 *unexposed*) | | | | | | | | |
| Analog | 0/3 | — | 5/36 | 1.4<br>0.5–4.5 | 12/40 | 3.3<br>1.2–8.6 | 17/79 | 2.2<br>0.9–5.0 |
| Digital | 36/214 | 1.8<br>0.98–3.4 | 24/111 | 2.3<br>1.2–4.7 | 8/18 | 5.4<br>2.0–15 | 68/343 | 2.1<br>1.2–3.8 |
| Cordless | 29/170 | 2.0<br>1.05–3.7 | 22/100 | 2.6<br>1.3–5.3 | 9/35 | 2.9<br>1.2–7.1 | 60/305 | 2.3<br>1.3–4.0 |

Unconditional logistic regression analysis adjusted for age, sex, SEI, and the year of diagnosis was used.

high-grade astrocytoma for analog and digital cellular telephones and cordless phones, but not significantly so for low-grade astrocytoma (Hardell et al., 2003a). These results are in agreement with the present findings.

The reporting of new cancer cases to the Swedish Cancer Registry is compulsory. Also, certain benign diseases such as benign brain tumors are reported. As soon as the histopathological diagnosis is obtained the respective pathological departments send a report to the local cancer registry in the five medical regions in Sweden. In addition, the treating physician makes a clinical report. Thus, a high reporting frequency is obtained with good coverage of all new cases, and no selection bias as to reporting exists.

Exposure was assessed by a questionnaire as in our previous study. The median time from date of diagnosis until the sending of the questionnaire was 68 days. This lag time included reporting from the cancer registry and obtaining permission from the treating physician to contact the patient. This lag time between the diagnosis and the interview is of potential benefit compared with a bedside interview since the patient has been informed about the diagnosis, possible further treatment, etc. The situation is also more relaxed at home than in the hospital and similar to the situation for the controls. For ethical reasons and in order to get more valid data, we prefer to conduct the interviews some weeks after the diagnosis instead of bedside, as in some other studies (Muscat et al., 2000; Inskip et al., 2001). One disadvantage of not conducting bedside interviews at hospitals might, however, be the loss of cases, since the prognosis is poor for patients with malignant brain tumors. In one report, median survival was only 47 weeks for glioblastoma multiforme (Stark et al., 2005).

It has been argued that the exclusion of deceased cases would bias the results, giving a falsely increased risk for only living subjects (Boice and McLaughlin, 2002). As we have discussed elsewhere, it is hard to scientifically defend that assumption, since it would imply that the risk associated with the use of cellular telephones must be decreased among deceased cases (Hansson Mild et al., 2003). It is not likely that a risk factor among survivors of a disease is preventive for cases with an aggressive disease giving a bad prognosis. In the present study 187 patients with a malignant brain tumor were deceased. Most of them had high-grade astrocytoma. Excluding deceased cases would thus dilute the overall risk toward unity.

When we had received the answered questionnaires, all cases and controls were interviewed over the phone to verify and clarify different exposures. Furthermore, an additional letter was sent to all cases who reported having always used a fixed antenna in a car in order to exclude any misunderstanding of that question. Also,

Table 3
Number of exposed cases (Ca) with malignant brain tumor and controls (Co), odds ratios (OR), and 95% confidence intervals (CI) for the use of cellular or cordless telephones for tumor localizations in relation to the ear used during telephone calls

| Localization/type of telephone | All Ca/Co OR, CI | Ipsilateral Ca/Co OR, CI | Contralateral Ca/Co OR, CI | Ipsi/contralateral Ca/Co OR, CI |
|---|---|---|---|---|
| *Malignant* | | | | |
| Analog phone | 68/79 | 31/25 | 24/28 | 9/14 |
| | 2.6 | 3.1 | 2.6 | 1.6 |
| | 1.5–4.3 | 1.6–6.2 | 1.3–5.4 | 0.6–4.4 |
| Digital phone | 198/343 | 97/108 | 59/124 | 28/41 |
| | 1.9 | 2.6 | 1.3 | 2.1 |
| | 1.3–2.7 | 1.6–4.1 | 0.8–2.2 | 1.1–3.9 |
| Cordless phone | 171/305 | 86/97 | 54/99 | 17/43 |
| | 2.1 | 2.9 | 1.7 | 1.1 |
| | 1.4–3.0 | 1.8–4.7 | 1.05–2.8 | 0.5–2.3 |
| *Astrocytoma, high grade* | | | | |
| Analog phone | 52/79 | 22/25 | 20/28 | 8/14 |
| | 3.6 | 4.2 | 5.4 | 2.8 |
| | 1.9–6.5 | 1.9–9.4 | 2.2–13 | 0.9–8.3 |
| Digital phone | 129/343 | 65/108 | 38/124 | 22/41 |
| | 2.2 | 3.2 | 1.6 | 3.5 |
| | 1.4–3.3 | 1.9–5.6 | 0.9–2.9 | 1.6–7.7 |
| Cordless phone | 106/305 | 60/97 | 31/99 | 11/43 |
| | 2.4 | 4.0 | 2.1 | 1.5 |
| | 1.5–3.7 | 2.2–7.0 | 1.1–3.9 | 0.6–3.4 |
| *Astrocytoma, low grade* | | | | |
| Analog phone | 5/79 | 3/25 | 1/28 | 1/14 |
| | 1.2 | 2.3 | 0.3 | 1.6 |
| | 0.3–4.9 | 0.4–14 | 0.03–3.7 | 0.1–17 |
| Digital phone | 24/343 | 12/108 | 6/124 | 3/41 |
| | 1.4 | 1.7 | 0.7 | 0.9 |
| | 0.5–3.8 | 0.5–5.4 | 0.2–2.6 | 0.2–5.0 |
| Cordless phone | 27/305 | 10/97 | 10/99 | 5/43 |
| | 1.4 | 2.0 | 1.4 | 1.1 |
| | 0.5–3.7 | 0.6–6.6 | 0.4–4.5 | 0.2–5.4 |
| *Other malignant* | | | | |
| Analog phone | 11/79 | 6/25 | 3/28 | 0/14 |
| | 1.6 | 2.5 | 0.9 | — |
| | 0.6–4.4 | 0.7–8.5 | 0.2–4.2 | — |
| Digital phone | 45/343 | 20/108 | 15/124 | 3/41 |
| | 1.9 | 2.1 | 1.3 | 0.8 |
| | 0.9–3.9 | 0.9–5.1 | 0.5–3.3 | 0.2–3.6 |
| Cordless phone | 38/305 | 16/97 | 13/99 | 1/43 |
| | 2.1 | 2.0 | 1.5 | 0.3 |
| | 0.99–4.2 | 0.8–4.8 | 0.6–3.8 | 0.03–2.6 |

Ipsilateral, same side for tumor and phone; contralateral, opposite side; ipsi/contralateral, both ears used equally. Unconditional logistic regression analysis adjusted for age, sex, SEI, and the year of diagnosis was used. Note that the tumor site was missing for some cases and the matched control was excluded as well as controls with a missing corresponding case.

the ear used primarily during phone calls was verified by an additional letter designed to obtain information regarding the habit over the years, possible change of ear, to what extent each ear had been used, etc. In the assessment of exposure, case or control status was not disclosed during the interviews. All subjects were identified by a unique identification number. All information was coded, registered into data files, and analyzed twice, with the same results, thus avoiding bias during that process. This procedure was the same as that used in our previous study and has been discussed in detail in that presentation (Hardell et al., 2002a).

One option to validate the use of phones would be to get information on billing records from the phone companies. However, phone companies have been reluctant to release such information for business reasons. Furthermore, several persons may use corporate as well as personal phones, pay-as-you-talk cards are very common, and a personal registration of the phone may not exist, so such an approach has limited value.

Table 4
Number of exposed cases (Ca) and controls (Co), odds ratios (OR), and 95% confidence intervals (CI) for the use of cellular or cordless telephones

| | 1–5-year latency | | >5–10-year latency | | >10-year latency | | Total, >1-year latency | |
|---|---|---|---|---|---|---|---|---|
| | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI | Ca/Co | OR, CI |
| *Malignant* | | | | | | | | |
| Analog | 0/3 | — | 20/36 | 1.0<br>0.6–1.8 | 48/40 | 2.2<br>1.3–3.5 | 68/79 | 1.5<br>1.04–2.3 |
| Digital | 100/214 | 1.0<br>0.7–1.3 | 79/111 | 1.4<br>0.96–1.9 | 19/18 | 1.9<br>0.9–3.7 | 198/343 | 1.3<br>0.9–1.7 |
| Cordless | 83/170 | 1.1<br>0.8–1.5 | 58/100 | 1.2<br>0.9–1.8 | 30/35 | 1.5<br>0.9–2.5 | 171/305 | 1.4<br>1.02–1.8 |
| *Astrocytoma, high grade* | | | | | | | | |
| Analog | 0/3 | — | 14/36 | 1.2<br>0.6–2.4 | 38/40 | 2.5<br>1.5–4.2 | 52/79 | 1.9<br>1.2–2.9 |
| Digital | 56/214 | 0.9<br>0.6–1.3 | 58/111 | 1.7<br>1.1–2.5 | 15/18 | 2.2<br>1.1–4.7 | 129/343 | 1.4<br>0.98–2.1 |
| Cordless | 47/170 | 1.1<br>0.7–1.6 | 37/100 | 1.2<br>0.8–1.9 | 22/35 | 1.6<br>0.9–2.9 | 106/305 | 1.3<br>0.9–1.9 |

Unconditional logistic regression multivariate analysis adjusted for age, sex, SEI, and the year of diagnosis was used.

Table 5
Number of exposed cases (Ca) with malignant brain tumor and controls (Co), odds ratios (OR), and 95% confidence intervals (CI) for the use of cellular or cordless telephones for different combinations of phone use

| Combination | Malignant, all | | | Astrocytoma, high grade | | |
|---|---|---|---|---|---|---|
| | Ca/Co | OR | CI | Ca/Co | OR | CI |
| Analog only | 3/7 | 1.3 | 0.3–5.7 | 1/7 | 0.7 | 0.1–5.9 |
| Digital only | 60/117 | 1.8 | 1.1–2.9 | 38/117 | 2.0 | 1.1–3.4 |
| Cordless only | 45/103 | 1.9 | 1.1–3.1 | 24/103 | 1.9 | 1.01–3.5 |
| Analog + digital | 57/66 | 2.7 | 1.6–4.7 | 44/66 | 3.9 | 2.1–7.6 |
| Analog + cordless | 45/42 | 3.6 | 2.0–6.6 | 35/42 | 5.3 | 2.6–11 |
| Digital + cordless | 118/196 | 2.0 | 1.3–3.1 | 75/196 | 2.4 | 1.5–4.1 |
| Analog + digital + cordless | 37/36 | 3.5 | 1.8–6.6 | 28/36 | 5.1 | 2.4–11 |
| Total, any combination | 254/459 | 1.9 | 1.3–2.7 | 161/459 | 2.1 | 1.4–3.2 |

Unconditional logistic regression analysis adjusted for age, sex, SEI, and the year of diagnosis was used.

Our main finding was a significantly increased risk for high-grade astrocytoma for all three studied phone types. The OR increased both with the increasing number of hours of use and tumor latency period. The highest risk was found for a >10-year latency period. Since the inclusion period of cases was between July 1, 2000 and December 31, 2003, all phone types had been on the market for more than 10 years. This inclusion period entailed the calculation of the use of analog phones with longer latency periods. The risk increased further for analog phones using a >15-year latency period, although this was based on low numbers. The median latency period for all malignant brain tumors was for analog phones 12 years, for digital cellular phones 5 years, and for cordless phones 6 years. In a separate analysis of high-grade astrocytoma, the same latency periods were obtained, except for digital cellular phones, which had a 6-year median latency period. Thus, it is necessary with longer latency periods (tumor induction periods) than in some previous studies to make valid risk calculations (Auvinen et al., 2002; Inskip et al., 2001; Johansen et al., 2001; Muscat et al., 2000). Certainly, our results are of relevance as to carcinogenesis, and this is so far the first study with the possibility of investigating the risk among long-term users.

Tumor laterality in relation to the ear used during phone calls was analyzed according to the method we have described previously (Hardell et al., 2001, 2002a). The matched control was assigned the same side as the tumor of the corresponding case. A similar method is to split the control group into left and right side at random. We used both techniques and obtained very similar results and no significant differences. The results with the method used in our previous studies are presented

here. Also, this time the OR was highest for ipsilateral exposure, but interestingly contralateral exposure also yielded an increased risk that was most pronounced for analog phones. Thus, for high-grade astrocytoma both ipsilateral and contralateral use of analog phones yielded a significantly increased risk. Of course, contralateral use of the phone gives some exposure to the tumor area. With a longer latency period, as for analog phones, that exposure might increase the risk for brain tumors.

In this study there was no clear pattern of highest risk in the temporal area of the brain, in contrast to our previous findings (Hardell et al., 2002a, 2003a). One explanation might be that with a longer tumor induction period a carcinogenic effect from microwaves may exist for the entire brain, since obviously the entire brain is exposed during the telephone calls, although the greatest exposure is in the area close to the antenna (cf. discussion of laterality of brain tumors above). The position of the antenna varies for different phones and of course different persons hold the phone in various positions. Telephones with extensible antennas, used most often in the early days and therefore with the longest exposure duration, result in a different exposure pattern.

It is noteworthy that, although we used the same study methods, in total no significantly increased risk was found for low-grade astrocytoma and other malignant brain tumors, with oligodendroglioma being the largest group ($n = 39$). However, ipsilateral exposure yielded the highest OR in these calculations. There is currently no mechanistic model for a tumor induction or promoting effect of microwaves on brain tumors with different growth potential (Kundi et al., 2004).

In the multivariate analysis, analog and digital cellular as well as cordless phones were independent risk factors for malignant brain tumors. The risk was significantly increased for subjects who had used digital cellular or cordless phones only. Regarding analog phones, few subjects had used this phone type only. The risk was higher when different phone types were combined, especially when analog phones were combined either with digital cellular telephones or cordless phones, the latter mainly of the digital type. An interaction may exist between different types of microwaves or merely indicate a longer latency period with higher cumulative use in hours in the combination with analog phones.

Cordless telephones have lower power output than GSM phones. However, as discussed elsewhere (Hansson Mild et al., 2003), the GSM phone regulates the output power depending on the quality of transmission. Measurements show that, for instance, in the city of Stockholm the GSM 900 phones use only 4% of the maximum output power as a median value (Persson et al., 2002). Furthermore, the DTX function, which causes the phone to transmit with 217 pulses per second when one is talking but with only 2 pulses per second when listening, in principle causes a further reduction with a factor of up to two. Most GSM phones have less than 1 W output power instead of the allowed 2 W in the standard. Thus, the GSM phones have a median power of 10–20 MW, i.e., the same order of magnitude as the cordless phones. With the longer calling time with cordless telephones, cf. Table 1, the ''dose'' for cordless users is then even higher than that for GSM users.

There is a variation in the power level from mobile phones between urban and rural areas. This is caused by the adaptive power control in the cellular telephone, which is regulated by the distance between power 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, i.e., urban areas, which have a shorter distance between base stations. By classifying the place of residence in urban or rural areas we could demonstrate that for cellular telephones the risk increase in our previous study was highest for subjects living in rural areas (Hardell et al., 2005). In the current study no such tendency was found, which might be explained by the fact that no subjects lived in the two most densely populated areas in Sweden, two of six areas in total (data not shown).

Epidemiological research on the risk of brain tumors and the use of cellular and cordless phones is limited. In fact, no other study except our previous investigation has information on cordless phones (Hardell et al., 2002a, b, 2003a, b). Regarding cellular telephones, only three case–control studies and one cohort study exist. The main limitation in these studies is too short a follow-up for tumor induction. Two hospital-based case–control studies from the USA did not find an increased risk (Muscat et al., 2000; Inskip et al., 2001). However, both were inconclusive because of the short duration of use and short latency periods. In a registry-based case–control study from Finland a significantly increased risk was found for all brain tumors and glioma (Auvinen et al., 2002). The omission of corporate subscriptions, the short duration of use, and possible exposure misclassification gave limited evidence of an association. A Danish retrospective cohort study on private subscribers was inconclusive due to the exclusion of company users, exposure misclassification, and the insufficient duration of follow-up (Johansen et al., 2001). These studies are not further discussed here since they as well as experimental studies have been scrutinized elsewhere (Hansson Mild et al., 2003; Kundi, 2004; Kundi et al., 2004).

In summary our study showed an increased risk for malignant brain tumors associated with the use of analog and digital cellular telephones and cordless phones. The risk was highest for the most malignant brain tumors, high-grade astrocytoma. The risk increased

with both the latency period and the number of hours used for phone calls.

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## References

Auvinen, A., Hietanen, M., Luukonen, R., Koskela, R.S., 2002. Brain tumors and salivary gland cancers among cellular telephone users. Epidemiology 13, 356–359.

Boice J.D., Jr., McLaughlin, J.K., 2002. Epidemiologic Studies of Cellular Telephones and Cancer Risk—A Review. Statens Strålskyddsinstitut rapport (Swedish Radiation Protection Agency Report) 16, 2002. Available at URL http://www.ssi.se (accessed 14 February 2005).

Hansson Mild, K., Hardell, L., Kundi, M., Mattsson, M.-O., 2003. Mobile telephones and cancer: is there really no evidence of an association [see Review]? Int. J. Mol. Med. 12, 67–72.

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

Hardell, L., Hansson Mild, K., Påhlson, A., Hallquist, A., 2001. Ionising radiation, cellular telephones and the risk for brain tumours. Eur. J. Cancer Prev. 10, 523–529.

Hardell, L., Hallquist, A., Hansson Mild, K., Carlberg, M., Påhlson, A., Lilja, A., 2002a. Cellular and cordless telephones and the risk for brain tumours. Eur. J. Cancer Prev. 11, 377–386.

Hardell, L., Hansson Mild, K., Carlberg, M., 2002b. Case–control study on the use of cellular and cordless phones and the risk for malignant brain tumours. Int. J. Radiat. Biol. 78, 931–936.

Hardell, L., Hansson Mild, K., Carlberg, M., 2003a. Further aspects on cellular and cordless telephones and brain tumours. Int. J. Oncol. 22, 399–407.

Hardell, L., Hansson Mild, K., Carlberg, M., Hallquist, A., Påhlson, A., 2003b. Vestibular schwannoma, tinnitus and cellular telephones. Neuroepidemiology 22, 124–129.

Hardell, L., Hallquist, A., Hansson Mild, K., Carlberg, M., Gertzén, H., Schildt, E-B., Dahlqvist, Å., 2004. No association between the use of cellular or cordless telephones and salivary gland tumours. Occup. Environ. Med. 61, 675–679.

Hardell, L., Carlberg, M., Hansson Mild, K., 2005. Use of cellular telephones and brain tumour risk in urban and rural areas. Occup. Environ. Med. 62, 390–394.

Inskip, P.D., Tarone, R.E., Hatch, E.E., Wilcosky, T.C., Shapiro, W.R., Selker, R.G., Fine, H.A., Black, P.M., Loeffler, J.S., Linet, M.S., 2001. Cellular-telephone use and brain tumors. N. Engl. J. Med. 344, 79–86.

Johansen, C., Boice, J., McLaughlin, J.K., Olsen, J.H., 2001. Cellular telephones and cancer—a nationwide cohort study in Denmark. J. Natl. Cancer Inst. 93, 203–207.

Kundi, M., 2004. Mobile phone use and cancer. Occup. Environ. Med. 61, 560–570.

Kundi, M., Hansson Mild, K., Hardell, L., Mattsson, M.-O., 2004. Mobile telephones and cancer—a review of epidemiological evidence. J. Toxicol. Environ. Health B 7, 351–384.

Muscat, J.E., Malkin, M.G., Thompson, S., Shore, R.E., Stellman, S.D., McRee, D., Neugut, A.I., Wynder, E.L., 2000. Handheld cellular telephone use and risk of brain cancer. JAMA 284, 3001–3007.

Persson, T., Törnevik, C., Larsson, L.-E., Lovén J., 2002. GSM mobile phone output power distribution by network analysis of all calls in some urban, rural and in-office networks, complemented by test phone measurements. Twenty-Fourth Annual Meeting of the Bioelectromagnetics Society, pp. 181–183.

Stark, A.M., Nabavi, A., Mehdorn, H.M., Blomer, U., 2005. Glioblastoma multiforme-report of 267 cases treated at a single institution. Surg. Neurol. 63, 162–169.