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Pooled analysis of two case–control studies on use of cellular and cordless telephones and the risk for malignant brain tumours diagnosed in 1997–2003

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Abstract *Objectives*: To study the use of cellular and cordless telephones and the risk for malignant brain tumours. *Methods*: Two case–control studies on malignant brain tumours diagnosed during 1997–2003 included answers from 905 (90%) cases and 2,162 (89%) controls aged 20–80 years. We present pooled analysis of the results in the two studies. *Results*: Cumulative lifetime use for >2,000 h yielded for analogue cellular phones odds ratio (OR) = 5.9, 95% confidence interval (CI) = 2.5–14, digital cellular phones OR = 3.7, 95% CI = 1.7–7.7, and for cordless phones OR = 2.3, 95% CI = 1.5–3.6. Ipsilateral exposure increased the risk for malignant brain tumours; analogue OR = 2.1, 95% CI = 1.5–2.9, digital OR = 1.8, 95% CI = 1.4–2.4, and cordless OR = 1.7, 95% CI = 1.3–2.2. For high-grade astrocytoma using >10 year latency period analogue phones yielded OR = 2.7, 95% CI = 1.8–4.2, digital phones OR = 3.8, 95% CI = 1.8–8.1, and cordless phones OR = 2.2, 95% CI = 1.3–3.9. In the multivariate analysis all phone types increased the risk. Regarding digital phones OR = 3.7, 95% CI = 1.5–9.1 and cordless phones OR = 2.1, 95% CI = 0.97–4.6 were calculated for malignant brain tumours for subjects with first use <20 years of age, higher than in older persons. *Conclusion*: Increased risk was obtained for both cellular and cordless phones, highest in the group with >10 years latency period.

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Introduction

The issue of a potential association between cellular and cordless telephones, and health effects is of concern and has been discussed in several articles during recent years (Kundi 2004; Kundi et al. 2004). Since the use of these phone types is widespread and increasing in the society, also a small risk increase would result in several affected persons. Of special concern is the risk of brain tumours since this part of the body is highly exposed during phone calls compared with other parts.

The Nordic countries were among the first in the world to introduce cellular phones and this allows a fairly long follow-up of users to evaluate possible health consequences. The analogue (NMT, Nordic Mobile Telephone System) phones operating at 450 MegaHertz (MHz) were introduced in Sweden in 1981. First they were used in a car with a fixed external antenna, but from 1984 portable NMT 450 phones are available on the market. The next generation of analogue phones using 900 MHz (NMT 900) was used in Sweden between 1986 and 2000. The digital system (GSM, Global System for Mobile Communication) started in 1991 and has, during recent years, dramatically increased to be the most common phone type. This system uses dual band, 900 and 1,800 MHz, for communication. From 2003 the third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System) has started operating at 1 900 MHz in Sweden.

Cellular telephones emit radio frequency signals during calls. Exposure is characterized through the specific absorption rate (SAR) expressed as watt per kilogram. However, SAR differs in absolute values as well as in anatomical distribution between various types of cellular telephones, and information about SAR values was not available until most recent years.

Of interest in this context are also desktop cordless phones. First the analogue system in the 800–900 MHz RF range was used, but since 1991 digital cordless telephones (DECT) which operate at 1,900 MHz are on the market.

Since the brain is one of the most highly exposed organs for RF-field exposure during cellular and cordless phone calls, tumours with that localization are suitable to study. Acoustic neuroma might be a "signal" tumor for an association, since it is located in an area with the highest exposure. Furthermore, the risk would be higher for tumours on the same side of the head as the exposure to the RF-field (ipsilateral exposure).

In 1999 we published our first study on this topic with cases and controls from the time span 1994–1996 (Hardell et al. 1999). The analyses were based on answers from 209 (90%) of the cases and 425 (91%) of the controls. Overall we did not find an increased risk. However, for ipsilateral exposure we saw a somewhat higher risk, although based on a few exposed subjects (Hardell et al. 1999, 2001). Due to low numbers of exposed subjects and short latency periods no conclusions could be drawn from that study.

Our next case–control study was larger. The responding numbers were for cases 1,429 (88%) of those fulfilling the inclusion criteria and for controls 1,470 (91%). Both cases and controls were recruited during January 1, 1997 until June 30, 2000. We modified somewhat the questionnaire used in the first study to assess exposure as carefully as possible. Also more questions on other exposures of interest were added. For all brain tumours we found an increased risk for analogue phones that was most pronounced in the group with >10 year latency period, odds ratio (OR) 1.6, 95% confidence interval (CI) 1.1–2.5 (Hardell et al. 2003a). Moreover, the risk was highest for analogue and digital cellular telephones with ipsilateral exposure. This effect was most pronounced for high-grade astrocytoma. We found no association for meningioma. Regarding acoustic neuroma high risk was calculated for use of analogue phones, OR = 4.4, 95% CI = 2.1–9.2 (Hardell et al. 2003a, b).

Our third study was similar to the second study. In fact, the same questionnaire, methods and protocol were used in order to be able to pool these two studies to get a larger study material with longer time for use of both cellular and cordless phones. This study continued from July 1, 2000 until December 31, 2003. The study area consisted of Uppsala/Örebro and Linköping medical regions in Sweden. Stockholm and Gothenburg medical regions were not included this time since the WHO Interphone study on the same issue was performed during part of this time in these regions. Thus, there was no overlap of cases between any of our studies on this topic or the Interphone study (Hardell et al. 2003a, b, 2005a, b).

The aim of this presentation is to give the results of a pooled analysis of our second and third study on use of cellular and cordless telephones, and the risk for brain tumor. Here we present results for malignant brain tumours. All controls from the second and third studies are used as reference entity.

Materials and methods

We have, in our studies, presented details on the study methods (Hardell et al. 2003a, b, 2005a, b), so only a short presentation is given here. The ethical committees approved the studies. 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. Cases were reported in a consecutive way from the regional cancer registries, in total 3,729 patients. Subjects that did not meet the study prerequisites were excluded, i.e., brain metastases or wrong reporting to the registry ($n = 288$), wrong year for diagnosis ($n = 73$), missing histopathology ($n = 5$), not resident in study area ($n = 14$), deceased ($n = 745$), physician refusal ($n = 81$), not capable to participate ($n = 84$) and unknown address ($n = 2$), in total 1,292 cases. The final pooled study included 2,437 cases or 65% of those initially reported. Of these finally included cases 1,008 had a malignant brain tumor.

We draw one control subject matched on age and sex to each case from the Swedish population registry. They lived in the same geographical area (region) as the cases. The population registry covers the whole population with unique id-numbers and current address for all inhabitants. Any change of residence can be traced in the registry. Thus, 2 437 controls were recruited.

Assessment of exposure

The study was approved by the ethics committees and was performed in accordance with the ethical standards laid down by the Helsinki Declaration. All included persons had the possibility to refuse participation. We assessed different environmental and occupational exposures by using a 20-page questionnaire sent to the study subjects. It contained questions on the whole working history, exposure to different agents, smoking habits, etc. Regarding use of cellular telephones we asked about first year of use, type of phone (analogue with prefix 010, digital with prefix 07), mean minutes of daily use over the years, use in a car with external antenna or a hands-free (both calculated as unexposed), and ear most frequently used. Similar questions also dealt with use of cordless telephones.

If the questionnaire was not answered two reminders were sent. In order to verify exposures supplementary phone interviews were made in both studies by trained interviewers using the same structured protocol. We were careful to assess which ear was used most frequently over the years since a change might have occurred, e.g., in a case with acoustic neuroma. The interviewer checked this information but we also sent a letter and asked in both

studies all study subjects using cellular or cordless telephones to clarify this issue in detail.

We gave all questionnaires an id-code that did not show if it was a case or a control. Thus, interviews and coding of data for the statistical analysis were performed blinded as to case or control status. All cases had a diagnosis based on histopathological examination. We obtained such data from cancer registries and histopathological departments in the study area. Both clinical and pathology report were sent to the cancer registry in Sweden. Tumor localization was obtained by data in the cancer registries or if missing or unclear from neuroradiology investigations. We obtained copies of records after informed consent from the cases. Exposure ≤ 1 year before diagnosis was disregarded. Thereby the same year was used for the matched control as for the corresponding case.

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). Thereby the whole study population could be used in the statistical analyses adjusted for the matching variables. Subjects that had not used cellular or cordless phones were regarded as unexposed in the statistical calculations. The exposed cases and controls were divided according to phone type, analogue, digital, and cordless. We also calculated OR and 95% CI for use of any of these phone types and for different combinations. Adjustment was made for sex, age, socio-economic index (SEI)-code and year for diagnosis. Thereby the same year as for the case was used for the corresponding control. Adjustment for year of diagnosis was made in order to avoid bias in exposure since all controls, both malignant and benign brain tumor cases, were used in the analysis. We used age as a continuous variable in the analysis. Latency or tumor induction period was analysed using three time periods, >1–5, >5–10, and >10 years since first use of a cellular or cordless telephone until diagnosis. In the dose–response calculations median number of cumulative lifetime use in hours among controls was used as cut-off. Note that overall results for all latency groups were calculated in one analysis, whereas dose–response was analysed separately for each latency category.

Results

In total 905 (90%) cases and 2,162 (89%) controls participated. We display the results for cumulative use in hours for the different phone types (Fig. 1) and in total for any phone type in Table 1. Overall OR was highest in the group with longest duration of use, $>2{,}000$ h. Thus, analogue cellular phones yielded in that group OR = 5.9, 95% CI = 2.5–14, digital cellular phones OR = 3.7, 95% CI = 1.7–7.7, cordless phones OR = 2.3, 95% CI = 1.5–3.6, and total for any combination OR = 2.4, 95% CI = 1.7–3.4.

In Table 2 we give the results for the different phone types according to latency period and cumulative number of hours divided into two groups based on median number of hours among the controls. The risk increased with latency (Fig. 2) and duration of use. Thus, for all malignant brain tumours with >10-year latency period and in the highest exposure group we calculated for analogue cellular telephones (>85 h cumulative use) OR = 3.0, 95% CI = 2.0–4.5, digital cellular telephones

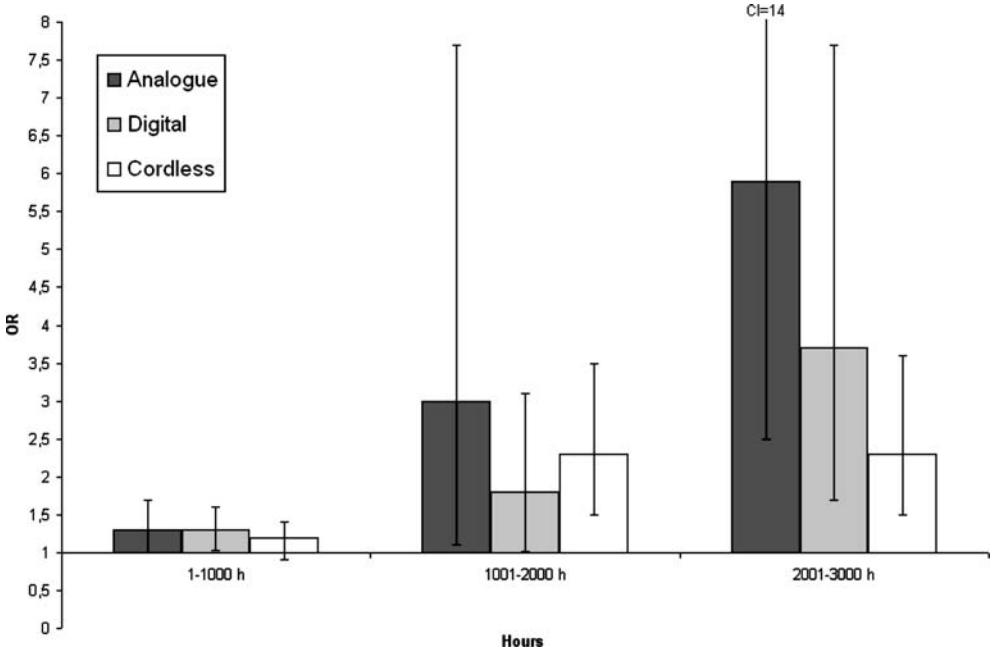

Fig. 1 Odds ratio (OR) and 95% confidence interval (CI) bars for three categories of cumulative use in hours (h) of analogue, digital, and cordless telephones, respectively. All malignant brain tumours

Table 1 Odds ratio (OR) and 95% confidence interval (CI) for cumulative lifetime use in hours of analogue and digital cellular telephones, cordless telephones and any combination of the three phone types. Number of exposed cases (Ca) and controls (Co) are given. Unconditional logistic regression analysis adjusted for age, sex, socio-economic index, and year of diagnosis was used. Test for trend yielded for analogue phones $P < 0.001$, digital $P = 0.01$, cordless $P < 0.001$, any combination $P < 0.0001$

	1–1,000 h			1,001–2,000 h			> 2,000 h		
	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Analogue	147/281	1.3	1.0002–1.7	10/8	3.0	1.1–7.7	21/8	5.9	2.5–14
Digital	355/731	1.3	1.03–1.6	26/33	1.8	1.02–3.1	21/12	3.7	1.7–7.7
Cordless	265/599	1.2	0.9–1.4	42/52	2.3	1.5–3.5	43/50	2.3	1.5–3.6
Total, any combination	433/983	1.2	0.98–1.4	65/104	1.6	1.1–2.2	85/85	2.4	1.7–3.4

Table 2 Number of exposed Ca with malignant brain tumour and Co, OR, and 95% CI for use of cellular or cordless telephones. Unconditional logistic regression analysis adjusted for age, sex, SEI, and year of diagnosis was used. In the dose–response calculations median number of cumulative use in hours among controls in the total material was used as cut-off

	> 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 ($n = 905$, 322 unexposed)								
Analogue	39/86	1.2 0.8–1.8	57/127	1.1 0.8–1.6	82/84	2.4 1.6–3.4	178/297	1.5 1.1–1.9
≤ 85 h	29/67	1.1 0.7–1.8	32/63	1.3 0.8–2.1	12/26	1.2 0.6–2.4	73/156	1.2 0.9–1.7
> 85 h	10/19	1.1 0.5–2.5	25/64	0.9 0.5–1.5	70/58	3.0 2.0–4.5	105/141	1.7 1.3–2.4
Digital	265/581	1.2 0.96–1.5	118/177	1.7 1.2–2.2	19/18	2.8 1.4–5.7	402/776	1.3 1.1–1.6
≤ 64 h	155/349	1.2 0.97–1.6	33/70	1.4 0.9–2.1	0/0	-	188/419	1.2 0.98–1.6
> 64 h	110/232	1.1 0.9–1.5	85/107	1.9 1.3–2.8	19/18	2.8 1.4–5.7	214/357	1.4 1.1–1.8
Cordless	193/437	1.2 0.9–1.5	124/219	1.5 1.1–2.0	33/45	1.8 1.1–3.0	350/701	1.3 1.1–1.6
≤ 195 h	105/260	1.1 0.8–1.4	30/74	1.1 0.7–1.8	3/17	0.4 0.1–1.5	138/351	1.0 0.8–1.3
> 195 h	88/177	1.4 0.99–1.8	94/145	1.8 1.3–2.5	30/28	3.3 1.8–5.9	212/350	1.6 1.3–2.1
Astrocytoma, high grade ($n = 539$, 198 unexposed)								
Analogue	21/86	1.3 0.8–2.2	35/127	1.3 0.8–2.0	59/84	2.7 1.8–4.2	115/297	1.7 1.3–2.3
≤ 85 h	13/67	1.0 0.5–1.9	22/63	1.6 0.96–2.8	8/26	1.4 0.6–3.3	43/156	1.3 0.9–2.0
> 85 h	8/19	1.9 0.8–4.7	13/64	1.0 0.5–1.9	51/58	3.7 2.3–5.9	72/141	2.2 1.5–3.2
Digital	143/581	1.3 0.97–1.7	86/177	2.2 1.6–3.1	15/18	3.8 1.8–8.1	244/776	1.5 1.2–1.9
≤ 64 h	90/349	1.4 1.01–1.9	22/70	1.6 0.9–2.8	0/0	-	112/419	1.4 1.04–1.8
> 64 h	53/232	1.2 0.8–1.7	64/107	2.9 1.9–4.4	15/18	3.8 1.8–8.1	132/357	1.7 1.3–2.3
Cordless	103/437	1.2 0.9–1.7	79/219	1.8 1.3–2.5	23/45	2.2 1.3–3.9	205/701	1.5 1.1–1.9
≤ 195 h	58/260	1.1 0.8–1.6	19/74	1.3 0.8–2.3	3/17	0.9 0.2–3.2	80/351	1.1 0.8–1.5
> 195 h	45/177	1.4 0.96–2.1	60/145	2.4 1.7–3.5	20/28	3.9 2.0–7.8	125/350	1.9 1.4–2.6
Astrocytoma, low grade ($n = 124$, 36 unexposed)								
Analogue	6/86	1.1 0.4–2.8	7/127	1.1 0.4–2.6	6/84	1.6 0.6–4.1	19/297	1.2 0.6–2.2
≤ 85 h	5/67	1.2 0.4–3.4	4/63	1.4 0.4–4.2	0/26	-	9/156	1.1 0.5–2.5
> 85 h	1/19	0.7 0.1–6.0	3/64	0.8 0.2–2.8	6/58	2.2 0.8–5.9	10/141	1.3 0.6–2.9
Digital	41/581	1.4 0.8–2.3	14/177	1.6 0.8–3.4	1/18	1.3 0.2–11	56/776	1.4 0.9–2.3

Table 2 (Contd.)

	> 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
≤ 64 h	24/349	1.5 0.9–2.7	3/70	1.2 0.3–4.3	0/0	-	27/419	1.5 0.8–2.6
> 64 h	17/232	1.2 0.6–2.3	11/107	1.7 0.7–4.1	1/18	1.3 0.2–11	29/357	1.3 0.7–2.4
Cordless	31/437	1.3 0.7–2.2	20/219	1.6 0.9–3.0	5/45	1.6 0.5–4.6	56/701	1.4 0.9–3.4
≤ 195 h	17/260	1.2 0.6–2.3	4/74	1.4 0.5–4.4	0/17	-	21/351	1.2 0.6–2.1
> 195 h	14/177	1.2 0.6–2.6	16/145	2.1 1.1–4.2	5/28	3.3 0.9–12	35/350	1.7 0.96–2.9
Other malignant (n = 242, 88 unexposed)								
Analogue	12/86	1.1 0.6–2.1	15/127	1.0 0.5–1.8	17/84	2.4 1.3–4.6	44/297	1.3 0.9–2.0
≤ 85 h	11/67	1.3 0.6–2.6	6/63	1.0 0.4–2.4	4/26	1.6 0.5–5.0	21/156	1.2 0.7–2.1
> 85 h	1/19	0.4 0.05–3.1	9/64	1.0 0.5–2.3	13/58	2.6 1.3–5.4	23/141	1.4 0.8–2.5
Digital	81/581	1.2 0.8–1.7	18/177	1.0 0.5–1.7	3/18	2.7 0.7–11	102/776	1.1 0.8–1.6
≤ 64 h	41/349	1.1 0.7–1.7	8/70	1.4 0.6–3.2	0/0	-	49/419	1.1 0.8–1.7
> 64 h	40/232	1.3 0.8–2.0	10/107	0.8 0.3–1.7	3/18	2.7 0.7–11	53/357	1.1 0.7–1.7
Cordless	59/437	1.2 0.8–1.8	25/219	1.1 0.6–1.7	5/45	1.1 0.4–2.9	89/701	1.2 0.8–1.7
≤ 195 h	30/260	1.1 0.7–1.7	7/74	1.0 0.4–2.3	0/17	-	37/351	1.0 0.6–1.5
> 195 h	29/177	1.5 0.9–2.4	18/145	1.0 0.6–1.8	5/28	2.4 0.8–7.4	52/350	1.4 0.9–2.0

(> 64 h cumulative use) OR = 2.8, 95% CI = 1.4–5.7, and cordless telephones (> 195 h cumulative use) OR = 3.3, 95% CI = 1.8–5.9. OR increased further for high-grade astrocytoma. We found high OR also for low-grade astrocytoma in the > 10-year latency group, but these results were based on low numbers of exposed cases. A similar tendency was found for other types of malignant brain tumours.

The group of other malignant brain tumours consisted of oligodendroglioma (n = 93), other/mixed gli-

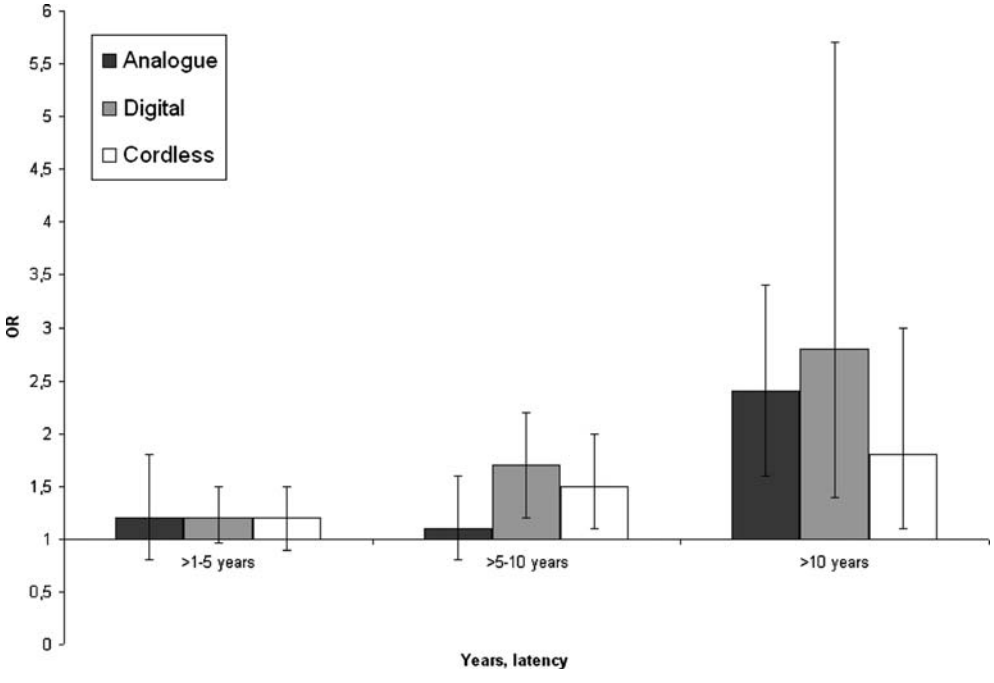

Fig. 2 Odds ratio and 95% CI bars for three categories of latency period for use of analogue, digital, and cordless telephones, respectively. All malignant brain tumours

oma ($n = 78$), and other malignant brain tumours ($n = 71$). Using >10-year latency period increased OR was found for these three groups but based on low numbers (data only shown for all).

As it can be seen in Table 3 we found consistently highest OR for ipsilateral exposure. This was most pronounced for high-grade astrocytoma yielding for analogue phones OR = 2.4, 95% CI = 1.6–3.6, digital phones OR = 2.3, 95% CI = 1.7–3.1, and cordless telephones OR = 2.0, 95% CI = 1.5–2.8.

In the multivariate analysis as displayed in Table 4 all of the studied phone types were associated with an increased risk for malignant brain tumours. For high-grade astrocytoma we found increased OR both in >5–10 and >10-year latency groups for digital cellular telephones and cordless phones, whereas for analogue phones OR increased only in the >10-year latency group.

Table 5 shows our analysis of OR for use of only one type of the different phone types and for different combinations. OR increased further for use of more than one type of the phones and was highest for the use of analogue, digital, and cordless phones, OR = 1.8, 95% CI = 1.2–2.6. These calculations yielded higher OR for high-grade astrocytoma. Only use of digital cellular phone gave for high-grade astrocytoma OR = 1.5, 95% CI = 1.1–2.0.

We analysed the association between use of cellular and cordless telephones for different age groups based on first use of the respective phone (Table 6). OR was highest for subjects in the <20 years age group for use of both digital and cordless telephones. Regarding analogue phones few subjects had started use <20 years of age.

Discussion

As it has been discussed elsewhere (Kundi 2004; Kundi et al. 2004) the main shortcoming of most of the so-far

Table 3 Number of exposed Ca with malignant brain tumour and Co, OR, and 95% CI for use of cellular or cordless telephones for tumour localisations in relation to ear used during phone calls. Ipsilateral = same side for tumour and phone, contralateral = opposite side, and ipsi/contralateral = both ears used much equally. Unconditional logistic regression analysis adjusted for age, sex, SEI and year of diagnosis, was used. Note that tumour site was missing for some cases and the matched control was excluded as well as controls with missing corresponding case

Localisation/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				
Analogue phone	178/297	95/98	54/100	20/35
	1.5	2.1	1.1	1.2
	1.1–1.9	1.5–2.9	0.8–1.6	0.7–2.2
Digital phone	402/776	195/240	119/266	54/84
	1.3	1.8	1.0	1.5
	1.1–1.6	1.4–2.4	0.7–1.3	1.004–2.2
Cordless phone	350/701	172/232	116/235	35/77
	1.3	1.7	1.1	1.1
	1.1–1.6	1.3–2.2	0.8–1.5	0.7–1.7
Astrocytoma, high grade				
Analogue phone	115/297	62/98	37/100	14/35
	1.7	2.4	1.6	1.5
	1.3–2.3	1.6–3.6	0.98–2.5	0.8–3.0
Digital phone	244/776	127/240	69/266	37/84
	1.5	2.3	1.1	2.1
	1.2–1.9	1.7–3.1	0.8–1.5	1.3–3.4
Cordless phone	205/701	113/232	63/235	20/77
	1.5	2.0	1.3	1.3
	1.1–1.9	1.5–2.8	0.9–1.8	0.7–2.3
Astrocytoma, low grade				
Analogue phone	19/297	10/98	4/100	4/35
	1.2	1.8	0.5	1.9
	0.6–2.2	0.8–4.1	0.2–1.6	0.6–6.2
Digital phone	56/776	27/240	16/266	6/84
	1.4	1.9	1.1	0.9
	0.9–2.3	1.02–3.5	0.5–2.1	0.3–2.5
Cordless phone	56/701	26/232	18/235	8/77
	1.4	1.9	1.1	1.4
	0.9–2.3	1.05–3.5	0.5–2.1	0.5–3.5
Other malignant				
Analogue phone	44/297	23/98	13/100	2/35
	1.3	1.9	0.9	0.5
	0.9–2.0	1.1–3.3	0.5–1.8	0.1–2.0
Digital phone	102/776	41/240	34/266	11/84
	1.1	1.2	1.0	1.0
	0.8–1.6	0.8–2.0	0.6–1.6	0.5–2.2
Cordless phone	89/701	33/232	35/235	7/77
	1.2	1.1	1.2	0.8
	0.8–1.7	0.7–1.7	0.7–1.8	0.3–1.8

Table 4 Number of exposed Ca and Co, OR, and 95% CI for use of cellular or cordless telephones. Unconditional logistic regression multivariate analysis adjusted for age, sex, SEI, and year of diagnosis was used

	>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								
Analogue	39/86	1.0 0.7–1.5	57/127	0.9 0.6–1.2	82/84	1.9 1.4–2.6	178/297	1.2 0.97–1.5
Digital	265/581	1.0 0.8–1.2	118/177	1.3 1.03–1.7	19/18	1.9 0.98–3.8	402/776	1.1 0.9–1.4
Cordless	193/437	1.0 0.8–1.2	124/219	1.3 0.98–1.6	33/45	1.3 0.8–2.0	350/701	1.1 0.9–1.3
Astrocytoma, high grade								
Analogue	21/86	1.0 0.6–1.6	35/127	0.9 0.6–1.4	59/84	2.0 1.4–2.9	115/297	1.3 1.001–1.7
Digital	143/581	1.0 0.8–1.2	86/177	1.7 1.2–2.3	15/18	2.4 1.1–4.9	244/776	1.3 1.03–1.6
Cordless	103/437	0.9 0.7–1.2	79/219	1.4 1.05–1.9	23/45	1.3 0.8–2.3	205/701	1.2 0.9–1.4

published studies on the association between cellular telephones and brain tumours is too short a latency period. Thus, both longer latency period and higher cumulative number of hours for use are necessary to get a more precise estimate of the risk. In our pooled study 96 cases with malignant brain tumor had used a cellular telephone (analogue and/or digital) for >10 years, and it should be noted that 33 cases had used a cordless phone for >10 years in our study.

Two case–control studies on brain tumours from USA (Muscat et al. 2000; Inskip et al. 2001), one from Denmark (Johansen et al. 2001) and one from Finland (Auvinen et al. 2002) did not report any cases with >10 years latency period for use of cellular telephones. In a Danish study on acoustic neuroma (Christensen et al. 2004) only two cases had used a cellular telephone with a latency period >10 years. A Swedish study on acoustic neuroma (Lönn et al. 2004) reported an increased risk in the group with >10 years latency period based on 14 cases. From the same study group results are now available on glioma and meningioma (Lönn et al. 2005) with 25 and 12 cases, respectively, with >10 years latency period.

In the latter Swedish study (Lönn et al. 2005) an increased risk was reported for glioma with OR = 1.6, 95% CI = 0.8–3.4 ($n = 15$ cases) and meningioma OR = 1.3, 95% CI = 0.5–3.9 ($n = 5$ cases) for ipsilateral exposure using >10 years latency period. On the other hand a somewhat decreased OR was reported for contralateral exposure but based on only 11 glioma cases and 3 meningioma cases. As we have discussed elsewhere (Hardell et al. 2005c) there are several methodological problems in the Lönn et al. (2005) study, such as numbers of cases not in agreement with the data in the Swedish Cancer registry, histopathological grading of more tumours than with available histopathology, and inclusion of cases and controls with exposure of the other side of the brain among unexposed in laterality analyses.

The Lönn et al. (2005) study is part of the WHO Interphone study. Regular use of cellular telephones gave a slightly decreased risk for glioma with OR = 0.8, 95% CI = 0.4–1.7. Interestingly the Danish part of the Interphone study produced OR = 0.6, 95% CI = 0.4–0.9 for high-grade glioma, in fact all 17 calculated ORs for high-grade glioma regarding latency, number of calls, hours of use, and intensity gave OR < 1.0 (Christensen et al. 2005). In Finland the Interphone study group reported OR = 0.6, 95% CI = 0.4–0.8 for brain tumours (Lahkola et al. 2005) and in Norway OR = 0.6, 95% CI = 0.4–0.9 for glioma (Klæbo 2005).

These results are contradictory to our findings and imply either protection against brain tumours from microwaves or methodological problems in the Interphone study. The study methods in the Interphone study were quite different from our study, e.g., computer-based face to face and even bedside interviews shortly after tumour diagnosis, multiple interviewers, uncertain diagnosis not all based on histopathology, disclosure of case or control status during interviews, inconsistent numbers in published tables, use of cordless phones not assessed, recruitment of some controls by phone calls (Klæbo 2005, Hardell et al. 2005c).

Certainly patients with brain tumour are a special group to be interviewed who differ from other cancer patients. Depression has been associated with brain tumours (Oksbjerg Dalton et al. 2002). Cognitive dysfunction including dementia has been reported in cancer patients (Heflin et al. 2005). However, the authors excluded brain cancer from the study "due to its direct effect on cognition". In fact, in the Danish Interphone study cases with glioma scored significantly lower than controls due to problems in recalling words (aphasia) and symptoms due to paralysis. In our studies use of cellular and cordless phones was assessed by questionnaires that were answered about 2 months after diagnosis when the patient was at home. This is a more relaxed situation than a stressful bedside interview.

Table 5 Number of Ca with malignant brain tumor and Co, OR, and 95% CI for use of cellular or cordless telephones for different combinations of phone use. Unconditional logistic regression analysis adjusted for age, sex, SEI, and year of diagnosis was used

	>1 year latency		
	Ca/Co	OR	CI
Malignant			
Analogue only	42/79	1.4	0.9–2.1
Digital only	149/312	1.3	0.99–1.6
Cordless only	115/272	1.3	0.99–1.7
Analogue + digital	112/173	1.5	1.1–2.1
Analogue + cordless	94/138	1.6	1.2–2.2
Digital + cordless	211/384	1.4	1.1–1.8
Analogue + digital + cordless	70/93	1.8	1.2–2.6
Total, any combination	583/1172	1.3	1.1–1.5
Astrocytoma, high grade			
Analogue only	20/79	1.1	0.6–1.9
Digital only	90/312	1.5	1.1–2.0
Cordless only	60/272	1.3	0.9–1.8
Analogue + digital	78/173	2.1	1.5–3.1
Analogue + cordless	69/138	2.3	1.6–3.4
Digital + cordless	128/384	1.7	1.2–2.3
Analogue + digital + cordless	52/93	2.7	1.7–4.1
Total, any combination	341/1172	1.4	1.1–1.7

Table 6 Odds ratio and 95% CI in different age groups first use of cellular or cordless telephones. Numbers of exposed Ca and Co are given. Unconditional logistic regression analysis adjusted for age, sex, SEI, and year of diagnosis was used

	> 1 year latency		
	Ca/Co	OR	95% CI
Analogue phone			
All ages	178/297	1.5	1.1–1.9
<20	4/6	1.3	0.3–4.9
20 to 49	131/214	1.4	1.1–1.9
50 to 80	43/77	1.6	1.02–2.4
Digital phone			
All ages	402/776	1.3	1.1–1.6
<20	16/9	3.7	1.5–9.1
20 to 49	229/445	1.3	0.99–1.6
50 to 80	157/322	1.3	1.02–1.7
Cordless phone			
All ages	350/701	1.3	1.1–1.6
<20	17/16	2.1	0.97–4.6
20 to 49	200/416	1.2	0.9–1.5
50 to 80	133/269	1.5	1.1–1.9

From a biological view it is unlikely that microwave radiation protects against malignant brain tumours, so the results in the Interphone study indicate methodological problems. Furthermore, the Interphone study showed a statistically significantly increased risk for acoustic neuroma after 10 years ipsilateral use of a cellular phone, OR = 1.8, 95% CI = 1.1–3.1. Cases with acoustic neuroma are in a rather healthy group compared with malignant brain tumours (Schoemaker et al. 2005). Thus, so far the Interphone study shows both statistically significantly increased and decreased risks for brain tumours.

According to Table 1 in our pooled study, it is obvious that a fairly high number of lifetime cumulative use of cellular or cordless telephones is necessary to get a stable risk estimate. Thus, with >2,000 h of cumulative use we found a high risk and ORs in that range are usually hard to explain by undetected bias or confounding in a case–control study. There are no other studies with data on cumulative use for >2,000 h. The numbers of hours for grouping of use of cellular and cordless telephones were arbitrary chosen since there is no biological cut-off for exposure. However, of interest is the statistically significant trend test. It might also be argued that 2,000 h roughly corresponds to 10 years use in the work place for 1 h per day.

The reporting of new cancer cases to the Swedish cancer registry is compulsory. Furthermore certain benign diseases, such as benign brain tumours, 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.

Cases were reported in a consecutive way to us from the cancer registries in the included medical regions, and we have no indication of selection bias in this respect. For inclusion it was necessary to have histopathological verification of the diagnosis. If information was unclear or missing in the cancer registry we obtained copies of records from the pathology and radiology departments.

All exposure was assessed and coded in a blinded manner as to case or control status so as to avoid observational bias, as we have discussed in more detail elsewhere (Hardell et al. 2002). Misclassification of exposure may occur if cases recall exposure different to controls. Cordless telephones have not been discussed as a risk factor for brain tumours in the population, so also the results for that phone type indicate that recall bias may not explain the results. OR increased both with latency period and cumulative number of hours for use. The concepts of tumor induction period and dose–response are generally not understood in the population so these results strengthen our results and argue against recall bias as an explanation of the findings.

In the analyses we adjusted for sex since all controls were used and they were frequency matched to the cases. It should be noted that meningioma is more commonly occurring among females (Whittle et al. 2004) so sex might be a confounder, since the use of both cellular and cordless phones differs among men and women. Certainly the use is also age dependant, generally use of a phone is more common among younger persons, so adjustment was made for age in the calculations of OR and 95% CI. Another factor to take into account is year for diagnosis of the cases and corresponding year for the controls since this pooled analysis encompassed cases and controls recruited during 1997–2003 and the use of both cellular and cordless telephones increases over the

years. Finally, we also adjusted for current or last reported SEI-code since social class has been reported to be a determinant for brain tumours (Preston Martin and Mack 1996).

It has been argued that use of cordless phones should not be assessed since they 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 Stockholm city the GSM 900 phones only use 4% of the maximum output power as a median value (Persson et al. 2002). Furthermore, the DTX function which makes the phone transmit with 217 pulses per second when one is talking, but only with 2 pulses per second when listening, in principle causes a further reduction with a factor of up to two. Most GSM phones have less than 1 watt peak output power instead of the allowed 2 watt in the standard. Thus, the GSM phones have a median power of 10–20 mwatt, i.e., the same order of magnitude as the cordless phones. With the longer calling time with cordless telephones (c.f. Table 2) the "dose" for cordless users is then even higher than for that of the GSM users.

The mechanism for a carcinogenic effect from RF fields has been discussed for several years. Some studies have shown biological effects in experimental studies, whereas these findings have not been replicated in others (Kundi 2004; Kundi et al. 2004). Of interest is findings of genotoxic effects in cell systems exposed to radio frequency electromagnetic fields (RF-EMF) in the recently presented REFLEX-study (REFLEX final report 2005; Diem et al. 2005). In the REFLEX-study SAR levels which varied between 0.3 and 2 watt/kg were used. Increase in single and double strand DNA breaks and micronuclei frequency was found. Findings of chromosomal aberrations were observed in fibroblasts and intracellular increase of free radicals in HL-60 cells. It was concluded that RF-EMF might activate several groups of genes that play a role in cell division, cell proliferation, and cell differentiation. These results indicate pathophysiological mechanisms that could be the basis for the development of chronic diseases, such as cancer, in humans. Based on these results and our findings it must be concluded that the current allowed SAR level of 2 watt/kg based on thermal effects from RF-EMF is not appropriate.

In summary, this pooled analysis showed consistently increased risk for malignant brain tumours using >10 years latency period. Especially high OR was found for high-grade astrocytoma. OR increased with cumulative lifetime number of hours of use of analogue and digital cellular telephones and cordless phones. In multivariate analyses increased risk was found for all three phone types. OR was highest for ipsilateral use which is also of biological relevance. Of special concern is the higher risk for use of digital cellular telephones and cordless phones in the age group <20 years at start. However, these results are based on low numbers and need to be confirmed in further studies. Since the use of cellular and cordless telephones has increased during most recent years it is too early to detect a change of brain tumour incidence in cancer registries. Risk estimates and exposure frequencies in our studies enable calculation of the attributable fraction (AF); that is the proportion of cases that can be attributed to the particular exposure. This was calculated as the exposed case fraction multiplied by [(OR-1)/OR]. For use of cellular or cordless telephones in any combination AF was calculated to 15% based on the results in Table 5.

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