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Cellular and cordless telephones and the risk for brain tumours

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Microwave exposure from the use of cellular telephones has been discussed in recent years as a potential risk factor for brain tumours. We included in a case–control study 1617 patients aged 20–80 years of both sexes with brain tumour diagnosed between 1 January 1997 and 30 June 2000. They were alive at the study time and had histopathologically verified brain tumour. One matched control to each case was selected from the Swedish Population Register. The study area was the Uppsala-Örebro, Stockholm, Linköping and Göteborg medical regions of Sweden. Exposure was assessed by a questionnaire that was answered by 1429 (88%) cases and 1470 (91%) controls. In total, use of analogue cellular telephones gave an increased risk with an odds ratio (OR) of 1.3 (95% confidence interval (CI) 1.02–1.6). With a tumour induction period of >10 years the risk increased further: OR 1.8 (95% CI 1.1–2.9). No clear association was found for digital or cordless telephones. With regard to the anatomical area of the tumour and exposure to microwaves, the risk was increased for tumours located in the temporal area on the same side of the brain that was used during phone calls; for analogue cellular telephones the OR was 2.5 (95% CI 1.3–4.9). Use of a telephone on the opposite side of the brain was not associated with an increased risk for brain tumours. With regard to different tumour types, the highest risk was for acoustic neurinoma (OR 3.5, 95% CI 1.8–6.8) among analogue cellular telephone users. © 2002 Lippincott Williams & Wilkins.

Key words: Benign, brain tumours, cordless telephones, malignant, mobile telephones, temporal area.

Introduction

Ionizing radiation is an established risk factor for brain tumours with the highest risk for meningioma (Soffer *et al.*, 1989; Preston-Martin and Mack, 1996). Such radiation is genotoxic and causes damage to DNA either directly or indirectly through free radical formation.

The increasing use of cellular telephones has raised concerns about an increased risk for brain tumours. Radiofrequency (RF) signals are transmitted and received in the range of 800–4000 MHz. In Sweden, the analogue system (Nordic Mobile Telephone System; NMT) was introduced in 1981 operating at 450 MHz. Typically, in the beginning these phones were used in a car with an external antenna, but from 1984 the first portable analogue phones became available. The analogue 900 MHz system started in 1986, but was closed down in 2000 in Sweden.

The digital system (Global System for Mobile Communication; GSM) started in 1991 and grew commercially from 1992 to be the most common phone at the end of the 1990s in Sweden.

The first cordless phones were available in Sweden in 1988. Initially the analogue system in the 800–900 MHz RF range was used. Now digital cordless telephones that operate at 1900 MHz are available.

RF signals from cellular and cordless phones fall within the microwave part of the electromagnetic spectrum. Increased numbers of DNA breaks in rats have been reported after exposure to 2450 MHz (Lai and Singh, 1995, 1996), although these results have not been confirmed in other studies (Malyapa *et al.*, 1997a,b, 1998). An increased incidence of lymphoma was found in genetically engineered mice exposed to pulsed 900 MHz RF radiation (Repacholi *et al.*, 1997). These findings have not been replicated yet, however.

Induction of micronuclei in human lymphocytes exposed *in vitro* to microwave radiation has been reported (Zotti-Martelli *et al.*, 2000; Tice *et al.*, 2002). Thus, exposure to non-ionizing radiation in the range

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of microwaves might cause genotoxic effects, leading to concerns about carcinogenesis.

A number of epidemiological studies have investigated a potential association between mobile phones and brain tumours. In the main, no associations have been found and these results are discussed later on. We have previously performed a case–control study on brain tumours including 233 patients and 466 controls. Also a number of other exposures such as lifetime work history, ionizing radiation and use of different agents have been assessed. We reported an increased risk for tumours in the temporal and occipital brain area in patients with ipsilateral use of a cellular phone (i.e. in the parts of the brain receiving highest exposure) (Hardell *et al.*, 1999a, 2000, 2001). In a multivariate analysis adjusting for other risk factors (i.e. medical diagnostic X-ray investigation of the head and neck and laboratory work), the risk was significantly increased with an odds ratio (OR) of 2.62 (95% confidence interval (CI) 1.02–6.71).

These results were based on low numbers of exposed subjects. Moreover, the study period 1994–1996 covered only very recent use of digital cellular telephones without a reasonable tumour induction period. Exposure to cordless phones was not assessed in that study.

We have now performed a new larger study with a longer latency period for tumour development relating to microwave exposure from cellular or cordless telephones. Thus, cases or controls from our previous study (Hardell *et al.*, 1999a, 2000, 2001) were not included in this study.

Materials and methods

The geographical study area was the Uppsala-Örebro, Stockholm, Linköping and Göteborg medical regions of Sweden and the study encompassed patients diagnosed during 1 January 1997 to 30 June 2000. Only incident cases of both sexes with brain tumour were included, aged 20–80 years at the time of diagnosis. They were reported to us consecutively from the four regional cancer registries in these medical regions. The criterion was that they should have a histopathological diagnosis and were alive at the study start. Each patient's physician was contacted for permission to include the patient in the study.

One control to each case was drawn from the population register. They were matched for sex and age and lived in the same geographical area (region) of Sweden as the cases. Matching on age was done in 5-year age groups and the control was selected at random from this group. Controls were only selected for the finally included living cases.

Assessment of exposure

The ethical committees approved the investigation. Information on exposure was assessed by a postal 21-page questionnaire sent to both cases and controls. Two reminders were sent. Telephone interviews were performed for 12 cases and 13 controls that did not want to fill in the questionnaire but still agreed to participate. The questionnaire was based on the one we had used in our first study on this topic. It included, among other things, lifetime work history, exposure to ionizing radiation, different agents such as organic solvents, pesticides, asbestos, reproductive history for women and heredity. Here we report the results for cellular and cordless telephones.

Each study subject received a unique ID number that did not indicate whether it was a case or control. If the answers were unclear, a nurse trained for this purpose supplemented the answers over the telephone. A written protocol was used during the phone interviews. After that all the answers were scrutinized in order to be sure that uniform assessment of exposure for all subjects was obtained. If the quality of the answers was judged to fulfil our criteria for assessment of exposure, the information was coded and registered for statistical analysis. Otherwise the questionnaire was returned to the interviewer for additional telephone interview.

For cellular telephones questions were asked on type of phone, years of use and brand name. Also the first part of the phone number (prefix) was asked for so as to check if it was an analogue (010) or digital (070) phone. Specific questions were asked for each type of telephone: analogue 450 MHz or 900 MHz cellular phones, digital phones and cordless phones. This was important since people who need a cellular telephone (e.g. in their work) may use different types over the years. Mean number and length of daily calls in minutes were asked for and then cumulative use in hours for all years was calculated. Data were also collected on use in a car with fixed external antenna or hands-free device with an earpiece outside a car – both were taken as giving no exposure to microwaves. In one question respondents were asked which ear they used most frequently during cellular phone calls, or if both sides were used equally.

The questions on cordless phones asked about the number of years of use, mean number of minutes per day and ear used in the same way.

Since several of these questions, typically the ear mostly used during phone calls, might be difficult for relatives to give valid answers to, we only included living cases and controls in this study.

Subjects that started use of a mobile or cordless phone within one year prior to diagnosis were regarded as unexposed. The same year was used for the matched control as for the corresponding case. Cumulative exposure was calculated in hours from the first year of use up to the year before diagnosis. If the first year was apparently incorrect (i.e. before the respective phone use was on the market), this was corrected during the interviews and coding of exposure.

Histopathology was obtained from the Cancer Registry either as a 'Snomed' code or a written statement. The anatomical site of the tumour in the brain was not always given in the Cancer Registry. Also spinal tumours, recurrent or metastatic disease were not always notified. In order to get an accurate diagnosis, year for diagnosis, and tumour localization copies of reports of neuroradiology investigations were requested from radiology units at different hospitals. This was done after informed consent from the cases. For many cases information on tumour localization was also available in the Cancer Registry report. Based on these copies we judged if the tumour was a new diagnosis or a recurrent disease and determined the anatomical localization of the tumour. Cases with a radiology diagnosis of the tumour prior to the study period were excluded (e.g. slowly growing tumours that were operated only some years after diagnosis). No patient without a histopathological diagnosis was included in the study. All coding of anatomical area for the tumour was done without knowing if the subject was exposed to cellular or cordless phones.

Statistical methods

Conditional logistic regression analysis for matched studies was used to calculate odds ratios (OR) and 95% confidence intervals (CI), (SAS Institute, Cary, NC, USA). Only complete pairs (1:1) were used. Thereby the risk for use of the analogue and digital system as well as cordless phones was calculated separately. The matched control was assigned the same anatomical localization as for the corresponding case in calculations of laterality of exposure. In a multivariate analysis the use of different types of cellular telephones and cordless phones was analysed together.

Table 1. Number of cases aged 20–80 years reported from regional oncology centres

Total reported	2561
Metastasis or localization other than brain based on oncology centre reports	133
Other localization or diagnosis than brain based on neuroradiology records	99
Year other than study period for diagnosis	58
Histopathology missing	4
Not resident in study area	14
Deceased	540
Permission to be included refused by treating physician	35
Unknown address	2
Not capable of participating for medical reasons as reported by case or relative	59
Total included in study	1617

Results

In Table 1 inclusion of the cases is displayed. In total 2561 cases were reported from the regional cancer registries. The largest exclusion was being deceased. In the end, 1617 (63%) cases fulfilled the inclusion criteria. Of these 1617 cases, 1429 (88%) answered the questionnaire and of the 1617 controls 1470 (91%) answered; in total 1243 men and 1656 women responded. The results were based on 1303 complete pairs. The median age for both cases and controls was 54 years.

Exposure to analogue phones was reported by 247 (17.3%) cases and 218 (14.8%) controls, digital 423 (29.6%) cases and 433 (29.5%) controls, cordless 402 (28.1%) cases and 396 (26.9%) controls. In the tables numbers of discardent pairs with exposed cases and controls are given.

Table 2 gives the results for use of cellular phones. A significantly increased risk was found for analogue telephones with an OR of 1.3 (95% CI 1.02–1.6) increasing to OR 1.4 (95% CI 1.04–1.8) with >5-year tumour induction period and OR 1.8 (95% CI 1.1–2.9) with >10-year latency period. No increased risk was found for digital telephones, whereas the risk was non-significantly increased for cordless phones with increasing latency period. A tendency of a dose–response effect was found for analogue phones in the group with >10-year latency period (P for trend $=0.63$).

Regarding the use of analogue cellular telephones, the data were further analysed for those using analogue 450 MHz only yielding OR 1.0 (95% CI 0.7–1.4). Correspondingly for 900 MHz only OR 1.4

Table 2. Odds ratio (OR) and 95% confidence interval (CI) for use of cellular or cordless telephones

	>1 year latency			>5 year latency			>10 year latency		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue									
450 MHz	77/67	1.1	0.8–1.6	63/43	1.5	0.99–2.2	31/16	1.9	1.1–3.5
900 MHz	137/96	1.4	1.1–1.9	77/56	1.4	0.98–1.9	22/12	1.8	0.9–3.7
All	188/148	1.3	1.02–1.6	120/88	1.4	1.04–1.8	46/26	1.8	1.1–2.9
≤85 h	114/88	1.3	0.99–1.8	60/36	1.7	1.1–2.6	8/6	1.4	0.5–4.0
>85 h	96/82	1.2	0.9–1.6	72/64	1.2	0.8–1.7	39/21	1.9	1.1–3.2
Digital	224/228	1.0	0.8–1.2	33/36	0.9	0.6–1.5	–	–	–
≤55 h	165/156	1.04	0.8–1.3	8/13	0.6	0.3–1.5	–	–	–
>55 h	130/143	0.9	0.7–1.2	26/24	1.1	0.6–1.9	–	–	–
Cordless	238/242	1.0	0.8–1.2	102/77	1.3	0.99–1.8	6/3	2.0	0.5–8.0
≤183 h	136/162	0.9	0.7–1.1	35/27	1.3	0.8–2.2	0/1	–	–
>183 h	161/139	1.1	0.9–1.4	71/54	1.3	0.9–1.9	6/2	3.0	0.6–14.9

Numbers of discordant pairs with exposed case (Ca) or control (Co) are given. Dose–effect calculations were made with median number of hours for controls as cut-off.

Table 3. Odds ratio (OR) and 95% confidence interval (CI) for different anatomical areas of the brain for exposure >1 year before diagnosis

	Analogue			Digital			Cordless		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Frontal ($n=467$)	59/56	1.1	0.7–1.5	78/84	0.9	0.7–1.3	71/84	0.8	0.6–1.2
Parietal ($n=108$)	15/15	1.0	0.5–2.0	24/14	1.7	0.9–3.3	25/19	1.3	0.7–2.4
Temporal ($n=389$)	65/32	2.0	1.3–3.1	53/56	1.0	0.7–1.4	71/71	1.0	0.7–1.4
>5-year latency	38/20	1.9	1.1–3.3	9/3	3.0	0.8–11.1	33/17	1.9	1.1–3.5
>10-year latency	13/5	2.6	0.9–7.3	–	–	–	2/2	1.0	0.1–7.1
Occipital ($n=50$)	3/5	0.6	0.1–2.5	6/9	0.7	0.2–1.9	6/8	0.8	0.3–2.2
Fronto-parietal ($n=78$)	13/12	1.1	0.5–2.4	13/8	1.6	0.7–3.9	15/9	1.7	0.7–3.8
Fronto-temporal ($n=65$)	5/4	1.3	0.3–4.7	13/10	1.3	0.6–3.0	9/10	0.9	0.4–2.2
Temporo-parietal ($n=30$)	3/4	0.8	0.2–3.4	4/4	1.0	0.3–4.0	6/3	2.0	0.5–8.0
Parieto-occipital ($n=41$)	6/4	1.5	0.4–5.3	9/7	1.3	0.5–3.5	4/12	0.3	0.1–1.03
Cerebellum ($n=86$)	8/8	1.0	0.4–2.7	12/18	0.7	0.3–1.4	18/10	1.8	0.8–3.9
Multiple/central ($n=44$)	5/3	1.7	0.4–7.0	4/5	0.8	0.2–3.0	4/5	0.8	0.2–3.0

Numbers of cases with different tumour localization and discordant pairs with exposed case (Ca) or control (Co) are given.

(95% CI 1.03–1.8) and for subjects using both types of phones (450 MHz and 900 MHz) OR 1.7 (95% CI 0.9–3.3) was calculated (data not shown in table).

For analogue 450 MHz cellular phones 60 cases and 64 controls had always used the cellular telephone in a car with fixed external antenna and they were regarded as unexposed. The corresponding numbers for analogue 900 MHz cellular phones were 11 cases and 25 controls. Regarding digital cellular phones two cases reported that they always used a fixed antenna in a car and one control had always used a hands-free device (with earpiece).

Anatomical localization of the tumour was available for 1358 patients. For 71 cases medical neuroradiology records were not obtained either due to lack of permission from the case ($n=44$) or because the respective radiology department did not respond to the request ($n=27$). Increased risk was found for cases with a tumour in the temporal area exposed to microwaves from analogue phones with OR 2.0 (95% CI 1.3–3.1) increasing to OR 2.6 (95% CI 0.9–7.3) in the group with >10-year latency period (Table 3). For digital telephones increased risk was found for >5-year latency period with OR 3.0 (95% CI 0.8–11.1). Since the study period ended on 30 June 2000 and the digital system was introduced in 1991 no subjects were exposed with a latency period of >10 years.

Cordless telephones also yielded an increased risk for tumours in the temporal area with latency >5 years with OR 1.9 (95% CI 1.1–3.5). Very few subjects had used a cordless phone with >10-year latency time.

Results for different anatomical parts of the tumour and side of head (ear) used during a call are given in Table 4. Regardless of type of phone, increased risk was found for tumour in the brain hemisphere with ipsilateral exposure; analogue phones OR 1.8 (95% CI 1.3–2.5), digital phones OR 1.3 (95% CI 0.99–1.8) and cordless phones OR 1.3 (95% CI 1.01–1.8). These results were also analysed for subjects who had used only one of these

Table 4. Numbers of discordant pairs with exposed case (Ca) or control (Co), odds ratio (OR) and 95% confidence interval (CI) for exposure to cellular or cordless telephones for different tumour localizations in relation to ear

Localization/Type of telephone	All Ca/Co OR (95% CI)	Ipsilateral Ca/Co OR (95% CI)	Contralateral Ca/Co OR (95% CI)	Ipsi/contralateral Ca/Co OR (95% CI)
Brain hemisphere				
Analogue phone	188/148	93/53	52/59	15/15
	1.3	1.8	0.9	1.0
	(1.02–1.6)	(1.3–2.5)	(0.6–1.3)	(0.5–2.0)
Digital phone	224/228	105/79	67/85	24/24
	1.0	1.3	0.8	1.0
	(0.8–1.2)	(0.99–1.8)	(0.6–1.1)	(0.6–1.8)
Cordless phone	238/242	111/83	65/92	26/29
	1.0	1.3	0.7	0.9
	(0.8–1.2)	(1.01–1.8)	(0.5–0.97)	(0.5–1.5)
Temporal area				
Analogue phone	65/32	30/12	25/17	9/3
	2.0	2.5	1.5	3.0
	(1.3–3.1)	(1.3–4.9)	(0.8–2.7)	(0.8–11.1)
Digital phone	53/56	24/22	21/25	8/9
	1.0	1.1	0.8	0.9
	(0.7–1.4)	(0.6–1.9)	(0.5–1.5)	(0.3–2.3)
Cordless phone	71/71	38/29	21/32	11/9
	1.0	1.3	0.7	1.2
	(0.7–1.4)	(0.8–2.1)	(0.4–1.1)	(0.5–2.9)
Other areas than temporal				
Analogue phone	117/111	63/41	27/42	5/12
	1.1	1.5	0.6	0.4
	(0.8–1.4)	(1.04–2.3)	(0.4–1.04)	(0.1–1.2)
Digital phone	163/159	81/56	45/59	16/15
	1.0	1.4	0.8	1.1
	(0.8–1.3)	1.03–2.0)	(0.5–1.1)	(0.5–2.2)
Cordless phone	158/160	73/54	44/60	15/20
	1.0	1.4	0.7	0.8
	(0.8–1.2)	(0.95–1.9)	(0.5–1.1)	(0.4–1.5)

Side of head (ipsilateral = same side; contralateral = opposite side; ipsi/contralateral = used both sides equal amount of time) used during a phone call. Latency period >1 year. Note, tumour site missing for a number of cases.

three phone types. This yielded for analogue cellular phones OR 1.4 (95% CI 0.7–2.8), digital cellular phones OR 1.4 (95% CI 0.8–2.6) and cordless phones OR 1.3 (95% CI 0.7–2.3).

For the temporal area and analogue phones the risk increased for ipsilateral use of the phone to OR 2.5 (95% CI 1.3–4.9). An increased risk was found also for parts (lumped together) other than the temporal area for both cellular and cordless phones for cases with ipsilateral exposure. Contralateral exposure consistently yielded no effect, except for the analogue cellular phone type for tumours in the temporal area with a non-significantly somewhat increased risk.

In Table 5 the histopathology types of the different brain tumours are listed. The only significant result was an increased risk for acoustic neurinoma and analogue phone use, with OR 3.5 (95% CI 1.8–6.8). All these tumours are located in the temporal area of the brain.

In Table 6 the same results are displayed for the temporal brain area. Analogue cellular microwave exposure yielded a non-significantly increased risk for malignant tumours, mainly astrocytoma, if a latency period of >10 years was applied. For digital and cordless telephones with >5 year latency period an increased risk was found for astrocytoma. Analogue phones gave increased risk for meningioma in the temporal area with OR 4.5 (95% CI 0.97–20.8).

Multivariate analysis of the whole material for analogue, digital and cordless phones was performed and the results are given in Table 7. The results were similar to those in the corresponding univariate analysis although with somewhat lower effect estimates (cf. Table 2).

Correlation coefficients were calculated for use of analogue and digital cellular phones for cases $r = 0.16$, controls $r = 0.18$, analogue cellular phones and cordless phones for cases $r = 0.21$, controls $r = 0.16$, and digital cellular phones and cordless phones for cases $r = 0.24$, controls $r = 0.24$. Thus use of these different phone types did not correlate well. These results indicate that the studied exposures may be independent risk factors.

Table 5. Odds ratio (OR) and 95% confidence interval (CI) for different histopathology types of brain tumours

	Analogue			Digital			Cordless		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Malignant (588)	79/70	1.1	0.8–1.6	112/99	1.1	0.9–1.5	104/92	1.1	0.9–1.5
Astrocytoma (415)	58/45	1.3	0.9–1.9	80/71	1.1	0.8–1.6	79/63	1.3	0.9–1.7
High-grade (335)	46/37	1.2	0.8–1.9	64/52	1.2	0.9–1.8	63/53	1.2	0.8–1.7
Low-grade (80)	12/8	1.5	0.6–3.7	16/19	0.8	0.4–1.6	16/10	1.6	0.7–3.5
Medulloblastoma (6)	2/1	2.0	0.2–22.1	3/0	–	–	1/0	–	–
Oligodendroglioma (54)	8/9	0.9	0.3–2.3	13/12	1.1	0.5–2.4	7/11	0.6	0.2–1.6
Ependymoma (11)	2/1	2.0	0.2–22.1	2/2	1.0	0.1–7.1	3/2	1.5	0.3–9.0
Other/mixed glioma (65)	5/9	0.6	0.2–1.7	9/10	0.9	0.4–2.2	9/9	1.0	0.4–2.5
Other (37)	4/5	0.8	0.2–3.0	5/4	1.3	0.3–4.7	5/7	0.7	0.2–2.3
Benign (841)	109/78	1.4	1.05–1.9	112/129	0.9	0.7–1.1	134/150	0.9	0.7–1.1
Meningioma (611[a])	60/56	1.1	0.7–1.5	78/102	0.8	0.6–1.03	90/105	0.9	0.6–1.1
Pituitary tumours (30)	7/9	0.8	0.3–2.1	5/4	1.3	0.3–4.7	4/6	0.7	0.2–2.4
Acoustic neurinoma (159[a])	38/11	3.5	1.8–6.8	23/19	1.2	0.7–2.2	30/29	1.0	0.6–1.7
Other (42)	4/2	2.0	0.4–10.9	6/4	1.5	0.4–5.3	10/10	1.0	0.4–2.4

[a]One case with both meningioma and acoustic neurinoma
Numbers of discordant pairs with exposed case (Ca) or control (Co) are given.

Table 6. Odds ratio (OR) and 95% confidence interval (CI) for different histopathology types of brain tumours in the temporal area

	Analogue			Digital			Cordless		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Malignant	16/19	0.8	0.4–1.6	18/22	0.8	0.4–1.5	25/16	1.6	0.8–2.9
>5 year latency	7/12	0.6	0.2–1.5	4/2	2.0	0.4–10.9	12/4	3.0	0.97–9.3
>10 year latency	4/2	2.0	0.4–10.9	–	–	–	0/1	–	–
Astrocytoma	14/11	1.3	0.6–2.8	15/14	1.1	0.5–2.2	21/12	1.8	0.9–3.6
>5 year latency	6/11	0.5	0.2–1.5	3/1	3.0	0.3–28.8	11/4	2.8	0.9–8.6
>10 year latency	3/2	1.5	0.3–9.0	–	–	–	0/1	–	–
High grade	13/8	1.6	0.7–3.9	12/11	1.1	0.5–2.5	17/12	1.4	0.7–3.0
>5 year latency	6/8	0.8	0.3–2.2	3/1	3.0	0.3–28.8	10/4	2.5	0.8–8.0
>10 year latency	3/1	3.0	0.3–28.8	–	–	–	0/1	–	–
Low grade	1/3	0.3	0.04–3.2	3/3	1.0	0.2–5.0	4/0	–	–
>5 year latency	0/3	–	–	0/0	–	–	1/0	–	–
>10 year latency	0/1	–	–	–	–	–	0/0	–	–
Oligodendroglioma	1/1	1.0	0.1–16.0	2/4	0.5	0.1–2.7	1/1	1.0	0.1–16.0
Other/mixed glioma	1/6	0.2	0.02–1.4	1/3	0.3	0.04–3.2	3/2	1.5	0.3–9.0
Other	0/1	–	–	0/1	–	–	0/1	–	–
Benign	49/13	3.8	2.0–6.9	35/34	1.0	0.6–1.7	46/55	0.8	0.6–1.2
>5 year latency	31/8	3.9	1.8–8.4	5/1	5.0	0.6–42.8	21/13	1.6	0.8–3.2
>10 year latency	9/3	3.0	0.8–11.1	–	–	–	2/1	2.0	0.2–22.1
Meningioma	9/2	4.5	0.97–20.8	11/14	0.8	0.4–1.7	14/25	0.6	0.3–1.1
>5 year latency	3/1	3.0	0.3–28.8	3/0	–	–	9/6	1.5	0.5–4.2
>10 year latency	1/1	1.0	0.1–16.0	–	–	–	0/0	–	–
Acoustic neurinoma	38/11	3.5	1.8–6.8	23/19	1.2	0.7–2.2	30/29	1.0	0.6–1.7
>5 year latency	26/7	3.7	1.6–8.6	2/1	2.0	0.2–22.1	11/6	1.8	0.7–5.0
>10 year latency	7/2	3.5	0.7–16.8	–	–	–	2/1	2.0	0.2–22.1
Other	2/0	–	–	1/1	1.0	0.1–16.0	2/1	2.0	0.2–22.1

Numbers of discordant pairs with exposed case (Ca) or control (Co) are given. Results are given for >1 year, for >5-year and for >10-year latency period.

Table 7. Multivariate analysis of exposure

	>1-year latency			>5-year latency			>10-year latency		
	Ca/Co	OR	CI	Ca/Co	OR	CI	Ca/Co	OR	CI
Analogue	188/148	1.3	1.04–1.6	120/88	1.1	0.8–1.6	46/26	1.3	0.8–2.3
Digital	224/228	1.0	0.8–1.2	33/36	0.9	0.6–1.5	–	–	–
Cordless	238/242	1.0	0.8–1.2	102/77	1.3	0.95–1.8	6/3	1.8	0.5–7.4

Numbers of discordant pairs with exposed case (Ca) or control (Co) are given.

Discussion

This population-based case–control study included patients with a histopathology diagnosis of brain tumour. Of the initially reported cases from the cancer registries only 61% fulfilled the inclusion criteria. This shows that adequate inclusion of cases with brain tumour is not obtained using cancer registry data without checking the diagnosis, thus giving selection bias. The lack of such an approach was exemplified in a letter on our first publication on cellular phones and brain tumours in which inclusion of our cases was questioned (Ahlbom and Feychting, 1999), but rebutted by us (Hardell *et al.*, 1999b), also by personal communication before they published their letter. We checked the completed Cancer Registry for that study period and we did find good agreement with our inclusion of 270 cases according to the study criteria (Table 8) (Hardell *et al.* 1999a, 2000, 2001). At the end of 1997 only 222 patients were alive. Ahlbom and Feychting reported 862 cases in the Cancer Registry compared with the correct number of 565 according to our inclusion criteria. Our interviews were performed during 1996–1997. It is clear that our included 270 living cases represent a correct number according to the Cancer Registry.

Different occupational and leisure time exposures were assessed by a questionnaire and the purpose of the study was not disclosed. Phone interviews and coding of the data were made blinded as to case or control status in order to reduce observational bias. Furthermore the material was coded and analysed twice in two separate data sets. Thereby the same results were obtained. Only living cases that were judged to be able to answer the questionnaire were included so as to get as high data quality as possible. Excluding deceased cases might bias the results if a risk factor is associated with a more aggressive tumour type with bad prognosis. However, there is no evidence that this should apply to microwave exposure from cellular or cordless phones.

Table 8. Numbers of cases aged 20–80 years reported to the Swedish Cancer Register and numbers of deceased during different time periods

Region	Total	Deceased			
		1994–1996	1994–1997	1994–1998	1994–1999
Uppsala-Örebro	300	189	237	252	259
Stockholm					
Malignant	176	71	101	109	117
Benign	89	5	5	6	8
Available cases	565	300	222	198	181

Total numbers are given for Uppsala-Örebro region (1994–1996, malignant only) and Stockholm region (1995–1996 malignant, 1996 benign). Youngest case included in the study was 21 years (Hardell *et al.*, 2001), but numbers are given according to inclusion criteria 20–80 years.

The main result in this study was an increased risk for brain tumours associated with the use of analogue cellular phones. Thus, these findings were similar to those previously reported by us for brain tumours (Hardell *et al.*, 1999a, 2000, 2001). In the present study the risk increased further with tumour induction period. Also for cordless phones an increased risk was found if tumour induction period of >5 years was applied. Furthermore these results were strengthened when tumours in the temporal area were analysed. Digital mobile phones also increased the risk if >5-year latency period was used.

Dose–effect calculations were made using the median number of hours for exposure among the controls. An effect was seen for analogue cellular phones and cordless phones if a latency period of >10 years was used. However, due to the different exposure depending on the localization of the antenna and different SAR values for different phones, cumulative exposure in hours seems not to be the most appropriate method. SAR hours would be preferable for calculation within the tumour area, but this is not possible with current information on exposure (cf. microTesla-years for exposure to extremely low frequency electromagnetic radiation, Hardell *et al.*, 1995).

The maximum microwave exposure from cordless phones is lower than that from cellular phones, which might give a lower risk. However such phones are usually used for longer calls than cellular phones. In our study the cumulative use in hours of cordless phones was 2–3 times longer (see Table 2) than for cellular telephones. This might be of importance for the effect estimates, which were higher than for digital cellular telephones. With regard to cellular phones, the analogue type has 3–4 times higher effect than the digital type. This may be of relevance to the different effect estimates found in this study for these phone types.

Furthermore, digital cellular phones have not been in use for as long as the analogue ones, which would be of importance for carcinogenesis. This was exemplified in our study with median time of use (tumour induction period) of 7 years for analogue phones, 3 years for digital phones and 5 years for cordless phones.

With regard to different tumours, the highest risk was found for acoustic neurinoma in cases with analogue phone use. This is a tumour type located in

an anatomical area exposed to microwaves when a phone is used on that particular ear. However, an increased risk for meningioma was also found, as well as for the whole group of benign tumours.

For malignant tumours, an increased risk was found for the three different phone types if a reasonable latency period was applied. However, no significant results were found (Table 6). These results were based on low numbers and must be interpreted with caution.

During a mobile phone call the highest microwave exposure occurs on the same side of the head as the phone is used with the highest exposure in the ipsilateral temporal area. There is a rapid decline in dose and the other side of the brain is exposed to a lower degree. OR was calculated for ipsilateral, contralateral or both ipsi- and contralateral exposure to microwaves from a mobile phone by combining data for both sides of the head. Interestingly increased risk was found for tumours in the hemisphere with highest exposure to microwaves (ipsilateral) regardless of phone type used. Consistently no risk was found for contralateral exposure (except for temporal lobe and analogue phones). Somewhat increased risk was also found for other parts of the brain than the temporal area when lumped together. However this category also included tumours in the frontotemporal and temporoparietal areas with higher exposure than in the frontal area.

In a case–control study it is always possible that cases report more exposure than controls. This could be the situation in a study on mobile phones and the risk for brain tumours. However, cordless phones have hardly been discussed in this context at all, so our findings of an increased risk for such use indicates that recall bias was not a major problem in the study. Also the finding of highest risk in the anatomical area most exposed, increasing risk with tumour induction period and cumulative exposure argue against recall bias. Patients do usually not have exact information about the tumour localization and concepts of latency and dose–response effects are not well understood in the population. Recall bias can never be completely excluded, of course, in a case–control study. As to reporting of ear during calls in relation to tumour site, some recall bias may have existed since several effect estimates were below unity for contralateral exposure.

The questionnaire gave the opportunity for the study subjects to give 'other information' at the end. We checked these reports to evaluate if use of a mobile phone was of concern as a risk factor among the cases. Only two cases expressed such concern. Most common was discussion of previous diseases ($n = 56$). The following potential risk factors were discussed by the cases: chemical exposure ($n = 51$), extremely low-frequency electromagnetic fields ($n = 28$), environment in general ($n = 20$), stress and psychosocial factors ($n = 12$), ionizing radiation ($n = 10$), heredity ($n = 9$), radon ($n = 8$), head injury ($n = 8$), video display unit ($n = 7$), exhaust ($n = 5$), Chernobyl fall-out ($n = 4$), electrical fields ($n = 4$), aspartame ($n = 4$), high noise-level ($n = 3$), radar ($n = 1$), microwave oven ($n = 1$) and lightning ($n = 1$).

One possibility for recall bias could be that subjects with a prior cancer diagnosis would report more exposure than others. In fact, the exposure frequency in that group was lower both for cases and controls compared with the cases and subjects that did not report a previous cancer (Table 9). It is also possible that relatives might overestimate exposure, but this was not the situation in this study (Table 10). These results further strengthen the conclusion that our results cannot be explained by recall bias.

Observational bias might have been introduced during the interviews. We checked exposure data in the questionnaires before and after interview (Table 11). Obviously the results were not affected

Table 9. Exposure among cases ($n = 176$) and controls ($n = 86$) reporting previous cancer diagnosis

	Previous cancer	No previous cancer
NMT		
Cases	25 (14.2%)	222 (17.7%)
Controls	12 (14.0%)	206 (14.9%)
GSM		
Cases	39 (22.2%)	384 (30.6%)
Controls	21 (24.4%)	412 (29.8%)
Cordless phones		
Cases	42 (23.9%)	360 (28.7%)
Controls	21 (24.4%)	375 (27.1%)

NMT, Nordic Mobile Telephone System; GSM, Global System for Mobile Communications.

Table 10. Exposure frequency among subjects with help from relatives, 456 cases, 137 controls, or no help, 936 cases, 1308 controls, to fill in the questionnaire. The question was not answered by 37 cases and 25 controls

	Help	No help
NMT		
Cases	65 (14.3%)	178 (19.0%)
Controls	15 (10.9%)	200 (15.3%)
GSM		
Cases	123 (27.0%)	289 (30.9%)
Controls	35 (25.5%)	395 (30.2%)
Cordless phones		
Cases	113 (24.8%)	281 (30.0%)
Controls	33 (24.1%)	357 (27.3%)

Table 11. Comparison of primary exposure (exp) data in the questionnaire and after supplementary interview

	Exp in questionnaire/ Unexp after interview	Unexp in questionnaire/ Exp after interview	Sum
NMT 450			
Cases	−20	+5	−15
Controls	−17	+4	−13
NMT 900			
Cases	−7	+6	−1
Controls	−9	+7	−2
GSM			
Cases	−3	+23	+20
Controls	0	+21	+21

Numbers are given for subjects reporting exposure in the questionnaire but regarded as unexposed after interview and vice versa.

by interviewer bias. Lack of exposure according to interview was mostly because the subjects had only used the phone in a car with external antenna.

In the analysis analogue, digital and cordless phones were calculated separately. However, in a multivariate analysis of the whole material similar results was obtained as in the univariate analysis. The risk was also calculated for tumours in the hemisphere of the brain with ispilateral exposure among subjects using only one phone type. Similar risks were obtained as in the whole material. This is in agreement with the results that use of one phone type did not correlate well with use of other types.

Some other studies have also investigated the use of mobile phones and risk for brain tumours (Muscat *et al.*, 2000; Inskip *et al.*, 2001; Johansen *et al.*, 2001). Overall no increased risk was found although an increased risk was reported for neuroepithelioma in one study as well as more ipsilateral mobile phone use among cases (Muscat *et al.*, 2000). A non-significantly increased risk was found for anaplastic astrocytoma and acoustic neurinoma in the other study from the USA (Inskip *et al.*, 2001). As we have discussed elsewhere, one major shortcoming of these studies is the short tumour induction period (Hardell *et al.*, 2001; Hardell and Hansson Mild, 2001a,b).

In summary our present study showed an increased risk for brain tumours among users of analogue cellular telephones. For digital cellular phones and cordless phones the results showed no significantly increased risk overall within a 5-year latency period.

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