Pooled analysis of case-control studies on malignant brain tumours and the use of mobile and cordless phones including living and deceased subjects

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Abstract. We studied the association between use of mobile and cordless phones and malignant brain tumours. Pooled analysis was performed of two case-control studies on patients with malignant brain tumours diagnosed during 1997-2003 and matched controls alive at the time of study inclusion and one case-control study on deceased patients and controls diagnosed during the same time period. Cases and controls or relatives to deceased subjects were interviewed using a structured questionnaire. Replies were obtained for 1,251 (85%) cases and 2,438 (84%) controls. The risk increased with latency period and cumulative use in hours for both mobile and cordless phones. Highest risk was found for the most common type of glioma, astrocytoma, yielding in the >10 year latency group for mobile phone use odds ratio (OR) = 2.7, 95% confidence interval (CI) = 1.9-3.7 and cordless phone use OR = 1.8, 95% CI = 1.2-2.9. In a separate analysis, these phone types were independent risk factors for glioma. The risk for astrocytoma was highest in the group with first use of a wireless phone before the age of 20; mobile phone use OR = 4.9, 95% CI = 2.2-11, cordless phone use OR = 3.9, 95% CI = 1.7-8.7. In conclusion, an increased risk was found for glioma and use of mobile or cordless phone. The risk increased with latency time and cumulative use in hours and was highest in subjects with first use before the age of 20.

Introduction

There has been a rapid development of wireless technology since the 1990s and nowadays most persons use mobile phones and cordless phones. Additionally, most populations are exposed to radiofrequency/microwave (RF) radiation emissions from wireless devices such as mobile phone base stations, broadcast transmission towers, pagers and personal digital assistants, wireless networks and other sources of RF radiation (1).

The brain is the target organ of the body with highest near field exposure to microwaves during use of a handheld wireless phone. Thus, fear of an increased risk for brain tumours from RF fields emitted from mobile phones has dominated the debate the last decade. Of equal importance is use of the desktop cordless phones.

Especially the ipsilateral brain (same side as the mobile phone has been used) is exposed, whereas the contralateral side (opposite side to the mobile phone) is much less exposed (2). Thus, for risk analysis it is of vital importance to have information on the localisation of the tumour in the brain and the side of the head that has been predominantly used during phone calls.

In studies of the risk of brain tumours related to use of wireless communication it is of outermost importance to have many cases with long latency time. The use of mobile phone has a long history in Sweden and therefore studies performed here offer good possibilities to study this question.

Analogue phones (Nordic Mobile Telephone System; NMT) were introduced on the market in the early 1980s using both 450 and 900 Megahertz (MHz) carrier waves. NMT 450 was used in Sweden since 1981 but closed down in December 31, 2007, whereas NMT 900 operated during 1986-2000.

The digital system (Global System for Mobile Communication; GSM) using dual band, 900 and 1,800 MHz, started to operate in 1991 and dominates the market now. The third generation of mobile phones, 3G or UMTS (Universal Mobile Telecommunication System), using 1,900-2,200 MHz RF broad band transmission was introduced worldwide during more recent years, in Sweden in 2003.

However, of equal importance for the exposure assessment as mobile phones is the use of the desktop cordless phones. These have been used in Sweden since 1988, first analogue 800-900 MHz RF fields, but since early 1990s the digital 1,900 MHz DECT (Digital Enhanced Cordless Telecommunications) system is used. The frequency used and output power from these devices are of the same order of magnitude

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as those of the GSM phones (3), and cannot be neglected in the total exposure assessment.

We have studied the association between use of wireless phones and brain tumours since the 1990s (4), for overview, see Hardell *et al* (5). In order to have as good assessment of exposure as possible only living cases and controls were included. The cases were interviewed a few months after the diagnosis. A number of cases, mostly with a malignant brain tumour, could not be included since they were deceased at that time.

Results for malignant brain tumours diagnosed during 1997-2003 have been published previously (6,7). Increased risk was found for use of both mobile and cordless phones, highest in the group with >10 years latency period, as also shown in an overview of all studies in this area (8). We have also published results for benign brain tumours in another report that showed an increased risk for acoustic neuroma whereas no pattern of an association was found for meningioma (9).

Exclusion of deceased cases was suggested to bias our results in a review commissioned by the former Swedish Radiation Protection Agency, now called the Swedish Radiation Safety Authority (10). The reason why such exclusion would bias the results was not given, but seemed to be an *ad hoc* hypothesis.

We decided to proceed with a case-control study on cases that had died before we could interview them. Since most of the deceased cases had a malignant brain tumour and overall no clear association was found for meningioma, the most common benign type, we decided to include only deceased cases with a malignant brain tumour. Our previous result of an association between mobile phone use and malignt brain tumours was confirmed (11).

Here we now present the results of a pooled analysis of our two large case-control studies on malignant brain tumours (6,12-14) and the study on deceased cases (11) so as to have a larger material for the analysis. All studies were approved by the regional ethics committee. The aim of this study is not to have a review of this research area, which can be found in other publications.

Materials and methods

Our three studies on this topic were of the case-control type. Exposures were assessed by mailed questionnaire, as described in more detail in the different publications.

The study included cases with a histopathological diagnosis of brain tumour during 1997-2003 aged 20-80 years at the time of the diagnosis. During January 1, 1997 until June 30, 2000 the study area covered Uppsala-Örebro, Stockholm, Linköping and Göteborg medical areas in Sweden whereas during July 1, 2000 until December 31, 2003 Uppsala-Örebro and Linköping regions were included. Cases were enrolled after we had received copies of the reports to the regional cancer registries. Tumour localisation was based on information in medical records and all tumour types were defined by using histopathology reports.

One living control person matched on age and sex was drawn to each living case from the Swedish population registry. This registry covers the whole population with unique id-numbers and current address for all inhabitants. All controls lived in the same geographical areas as the cases. In this pooled analysis all controls, even those controls to cases with benign brain tumour, were included in the unconditional logistic regression analysis.

Deceased controls to deceased cases were selected from the Death Registry in Sweden. One group consisted of controls that had died from other types of malignant diseases than brain tumour and one group included controls that had died from other diseases than cancer (11). Relatives to both cases and controls were identified through the Swedish Population Registry at the Swedish Tax Agency. This part covered the whole study period 1997-2003.

Different environmental and occupational exposures were assessed using a self-administered questionnaire that was sent to the living cases and controls or relatives to deceased subjects. Use of mobile and cordless phones was carefully assessed by a self-administered questionnaire. Life-time occupational history was assessed so as to be able to classify socioeconomic index (SEI) for cases and controls. The information was, if necessary, supplemented over the phone by a trained interviewer using a structured protocol.

The ear that had been mostly used, or equally both, during phone calls was assessed for living cases and controls. However, that information was regarded to be less reliable interviewing relatives so that part of the questionnaire was omitted for deceased subjects. Thus, the current analysis does not cover laterality of use of a wireless phone in relation to tumour localisation. Regarding living cases and controls such results can be found in our previous publications (6,12-14).

Latency period was defined using year of first use of a wireless phone and year of diagnosis (the same year for the matched control). Cumulative number of hours for use was calculated using number of years and average time used per day. Use in a car with external antenna was disregarded as well as use of a handsfree device. We adopted a minimum latency period of one year (≤1 year), and these subjects were included in the unexposed category.

All questionnaires were designed a unique id-number that did not reveal if it was a case or a control. All assessment of exposure and data coding was done blinded as to case or control status.

Statistical methods. Unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI). All analyses were done using Stata/SE 10.1 (Stata/SE 10.1 for Windows; Stata Corp., College Station, TX). The unexposed category consisted of subjects that reported no use of mobile or cordless phones, or exposure ≤1 year before reference date. The exposed cases and controls were divided according to phone type; analogue, digital, and cordless. The use of analogue and digital phones were analysed combined (i.e., mobile phone) in this presentation. Also results for all phone types combined (wireless phone) are presented.

Adjustment was made for sex, age (as a continuous variable), SEI-code and year for diagnosis. The same reference date (year) as for the case was used for the corresponding control. Adjustment for year of diagnosis was made in order to avoid bias due to the changing pattern of use of wireless phones

Table I. Descriptive data for adjustment factors and use of wireless phones (mobile phone and cordless phone combined).

	Cases			Controls		
	n, exposed	n, total	% exposed	n, exposed	n, total	% exposed
Total	727	1,251	58.1	1,267	2,438	52.0
Gender						
Men	487	728	66.9	643	1,078	59.6
Women	240	523	45.9	624	1,360	45.9
Age						
20-40	167	231	72.3	240	364	65.9
>40-60	355	527	67.4	727	1,162	62.6
>60	205	493	41.6	300	912	32.9
Year of diagnosis						
1997	127	271	46.9	204	524	38.9
1998	127	254	50.0	262	561	46.7
1999	135	249	54.2	225	455	49.5
2000	76	141	53.9	146	261	55.9
2001	82	111	73.9	128	203	63.1
2002	100	130	76.9	164	244	67.2
2003	80	95	84.2	138	190	72.3
SEI-code						
Blue-collar worker	297	563	52.8	527	1,132	46.6
White-collar worker	348	556	62.6	645	1,104	58.4
Self-employed	65	91	71.4	82	148	55.4
No work	17	41	41.5	13	54	24.1
Vital status						
Alive	583	905	64.4	1,172	2,162	54.2
Deceased	144	346	41.6	95	276	34.4

during the study period. Adjustment was also made for vital status (deceased or alive).

Latency (tumour induction period) was analysed using three time periods, >1-5 years, >5-10 years, and >10 years since first use of a mobile or a cordless phone until diagnosis. Median number of cumulative lifetime use in hours among controls was used as cut-off in the dose-response calculations. Results for different latency periods were calculated in one analysis, whereas dose-response calculations were made separately for each latency group. Lifetime use in hours was also divided in three groups, 1-1000, 1001-2000 and >2000 h to further explore the dose-response relations.

Results

Regarding living cases and controls in total 905 of 1,008 (90%) cases and 2,162 of 2,437 (89%) controls participated. Since unconditional logistic regression analysis adjusted for matching variables was used all controls could be included from the studies on the living subjects. Regarding deceased subjects answers were obtained from relatives to 346 of 464 (75%) cases and 276 of 463 (60%) controls without cancer as cause of death. Controls that had died from cancer were excluded from the present calculations so as to make the two control groups more similar. Furthermore, an association between RF exposure and other cancer forms can not be excluded, Hardell *et al* (11). Thus, the final sample consisted of 1,251 of 1,472 (85%) cases and 2,438 of 2,900 (84%) controls.

Descriptive data for the adjustment factors are given in Table I. Use of wireless phones differed depending on gender, age, year of diagnosis, SEI-code and vital status. These results were similar for cases and controls, although overall the exposure frequency was lower among the controls. The distribution of cases and controls was similar for the different years.

Table II. Odds ratio (OR) and 95% confidence interval (CI) for all malignant tumours and glioma and use of wireless phones.[a]

	>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
All malignant (n=1251)								
Wireless phone	300/697	1.0 0.9-1.2	265/421	1.4 1.1-1.7	162/149	2.1 1.6-2.8	727/1267	1.3 1.1-1.5
≤195 h	188/466	1.0 0.8-1.2	82/148	1.3 0.96-1.8	17/22	1.6 0.8-3.1	287/636	1.1 0.9-1.3
>195 h	112/231	1.1 0.9-1.5	183/273	1.4 1.1-1.8	145/127	2.4 1.7-3.2	440/631	1.5 1.2-1.8
Mobile phone	276/571	1.1 0.9-1.4	164/286	1.2 0.9-1.5	134/106	2.5 1.8-3.3	574/963	1.3 1.1-1.5
≤74 h	176/368	1.2 0.97-1.5	62/104	1.4 0.96-1.9	10/10	2.6 1.04-6.5	248/482	1.3 1.04-1.6
>74 h	100/203	1.0 0.8-1.4	102/182	1.1 0.8-1.5	124/96	2.7 1.9-3.7	326/481	1.3 1.1-1.6
Cordless phone	222/463	1.1 0.9-1.4	163/244	1.4 1.1-1.8	47/55	1.6 1.03-2.5	432/762	1.3 1.1-1.5
≤243 h	136/298	1.1 0.9-1.4	45/86	1.3 0.9-1.9	7/19	0.8 0.3-1.9	188/403	1.1 0.9-1.4
>243 h	86/165	1.2 0.9-1.7	118/158	1.7 1.3-2.2	40/36	2.3 1.4-3.9	244/359	1.5 1.2-1.8
Glioma (n=1148)								
Wireless phone	271/697	1.0 0.9-1.3	249/421	1.4 1.2-1.8	150/149	2.1 1.6-2.8	670/1267	1.3 1.1-1.5
≤195 h	171/466	1.0 0.8-1.3	76/148	1.3 0.98-1.8	14/22	1.4 0.7-2.8	261/636	1.1 0.9-1.3
>195 h	100/231	1.1 0.9-1.5	173/273	1.5 1.2-2.0	136/127	2.5 1.8-3.4	409/631	1.5 1.3-1.8
Mobile phone	250/571	1.1 0.9-1.4	156/286	1.3 0.99-1.6	123/106	2.5 1.8-3.3	529/963	1.3 1.1-1.6
≤74 h	163/368	1.3 0.996-1.6	60/104	1.4 1.004-2.1	8/10	2.2 0.8-5.8	231/482	1.3 1.1-1.6
>74 h	87/203	1.0 0.7-1.4	96/182	1.2 0.9-1.6	115/96	2.7 2.0-3.8	298/481	1.3 1.1-1.7
Cordless phone	205/463	1.2 0.9-1.5	152/244	1.5 1.2-1.9	45/55	1.7 1.1-2.6	402/762	1.3 1.1-1.6
≤243 h	124/298	1.1 0.9-1.4	41/86	1.3 0.9-2.0	7/19	0.8 0.3-2.1	172/403	1.1 0.9-1.4
>243 h	81/165	1.3 0.9-1.7	111/158	1.8 1.3-2.4	38/36	2.4 1.4-4.0	230/359	1.5 1.2-1.9
Astrocytoma (n=952)								
Wireless phone	208/697	1.0 0.8-1.3	212/421	1.5 1.2-1.9	133/149	2.3 1.7-3.0	553/1267	1.3 1.1-1.6
≤195 h	128/466	1.0 0.8-1.2	63/148	1.4 1.0004-2.0	14/22	1.7 0.8-3.5	205/636	1.1 0.9-1.3
>195 h	80/231	1.2 0.9-1.6	149/273	1.8 1.3-2.3	119/127	2.7 1.9-3.7	348/631	1.6 1.3-2.0

Table II. 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
Mobile phone	197/571	1.2	132/286	1.4	110/106	2.7	439/963	1.4
		0.9-1.5		1.04-1.8		1.9-3.7		1.2-1.7
≤74 h	126/368	1.3	48/104	1.5	8/10	2.7	182/482	1.3
		0.98-1.6		0.98-2.1		1.02-7.2		1.05-1.6
>74 h	71/203	1.1	84/182	1.3	102/96	3.1	257/481	1.5
		0.8-1.5		0.97-1.9		2.1-4.4		1.2-1.9
Cordless phone	157/463	1.2	135/244	1.7	41/55	1.8	333/762	1.4
		0.9-1.5		1.3-2.2		1.2-2.9		1.1-1.7
≤243 h	97/298	1.1	36/86	1.5	7/19	1.1	140/403	1.1
		0.8-1.5		0.96-2.3		0.4-2.7		0.9-1.5
>243 h	60/165	1.2	99/158	2.1	34/36	2.6	193/359	1.6
		0.9-1.7		1.5-2.8		1.5-4.5		1.3-2.1
Oligodendroglioma (n=102)								
Wireless phone	35/697	1.3	21/421	1.3	10/149	2.0	66/1267	1.4
		0.8-2.2		0.7-2.4		0.9-4.4		0.9-2.2
≤195 h	25/466	1.5	9/148	1.8	0/22	-	34/636	1.5
		0.9-2.6		0.8-4.0				0.9-2.5
>195 h	10/231	1.0	12/273	0.9	10/127	2.8	32/631	1.3
		0.5-2.1		0.5-2.0		1.2-6.5		0.7-2.1
Mobile phone	32/571	1.4	14/286	1.3	7/106	2.2	53/963	1.4
		0.8-2.4		0.7-2.6		0.9-5.4		0.9-2.3
≤74 h	23/368	1.7	7/104	2.0	0/10	-	30/482	1.7
		0.95-3.0		0.8-4.9				0.998-2.9
>74 h	9/203	1.0	7/182	0.8	7/96	2.8	23/481	1.2
		0.5-2.3		0.3-2.0		1.1-7.2		0.6-2.1
Cordless phone	26/463	1.4	9/244	1.0	3/55	1.4	38/762	1.3
		0.8-2.5		0.5-2.1		0.4-4.9		0.8-2.1
≤243 h	16/298	1.4	3/86	1.3	0/19	-	19/403	1.3
		0.7-2.7		0.4-4.4				0.7-2.3
>243 h	10/165	1.4	6/158	1.0	3/36	2.4	19/359	1.3
		0.7-3.1		0.4-2.4		0.6-9.2		0.7-2.4

[a]Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis and vital status. Cut-off of cumulative number of hours was based on median use among controls.

In Table II results are given for all malignant brain tumours and glioma. No statistically significantly increased risks were found in the latency group >1-5 years. Use of cordless phone yielded for all malignant tumours statistically significantly increased risk in the latency group >5-10 years and highest OR in the latency group >10 years and highest cumulative use; OR = 2.3, 95% CI = 1.4-3.9. For use of mobile phone the risk was statistically significantly increased in the >10 year latency group, in the category with >74 h cumulative use with OR = 2.7, 95% CI = 1.9-3.7. Most of the cases, 92%, had glioma and the results for this category were similar as overall.

Results for astrocytoma are presented in Table II and were in general similar to the whole glioma group. Risk increased with latency period and was highest in the group with highest cumulative use in hours with latency >10 years, for mobile phone OR = 3.1, 95% CI = 2.1-4.4 and for cordless phone OR = 2.6, 95% CI = 1.5-4.5. Note that some subjects could have used both a mobile and cordless phone, for further analysis see below.

Relatively few cases were diagnosed with oligodendroglioma (n=102) (Table II). Mobile phone cumulative use >74 h in the >10 year latency group yielded OR = 2.8, 95% CI 1.1-7.2,

Table III. Odds ratio (OR) and 95% confidence interval (CI) for malignant brain tumours and cumulative life time use in hours, per 100 h cumulative use and per year of latency of mobile and cordless phones.[a]

	1-1000 h		1001-2000 h		>2000 h		Per 100 h cumulative use	Per year of latency
	Ca/Co	OR, CI	Ca/Co	OR, CI	Ca/Co	OR, CI	OR, CI	OR, CI
All malignant (n=1251)								
Wireless phone	525/1052	1.2 0.98-1.4	79/117	1.4 1.04-2.0	123/98	2.4 1.8-3.3	1.013 1.008-1.018	1.054 1.036-1.073
Mobile phone	466/879	1.2 1.02-1.4	47/51	1.8 1.1-2.7	61/33	3.0 1.9-4.8	1.022 1.012-1.033	1.058 1.037-1.079
Cordless phone	320/643	1.1 0.9-1.4	53/60	2.0 1.3-3.0	59/59	2.1 1.4-3.1	1.011 1.004-1.018	1.045 1.019-1.071
Glioma (n=1148)								
Wireless phone	480/1052	1.2 0.98-1.4	74/117	1.5 1.1-2.1	116/98	2.5 1.8-3.5	1.014 1.008-1.019	1.056 1.037-1.075
Mobile phone	427/879	1.2 1.03-1.5	44/51	1.8 1.2-2.8	58/33	3.2 2.0-5.1	1.023 1.013-1.034	1.060 1.039-1.082
Cordless phone	297/643	1.2 0.95-1.4	50/60	2.0 1.4-3.1	55/59	2.2 1.4-3.2	1.012 1.004-1.019	1.049 1.023-1.075
Astrocytoma (n=952)								
Wireless phone	383/1052	1.2 0.98-1.4	67/117	1.7 1.2-2.4	103/98	2.8 2.0-3.9	1.015 1.009-1.021	1.063 1.043-1.084
Mobile phone	346/879	1.3 1.1-1.6	42/51	2.2 1.4-3.5	51/33	3.4 2.1-5.6	1.026 1.015-1.037	1.067 1.044-1.090
Cordless phone	240/643	1.2 0.96-1.5	45/60	2.3 1.5-3.6	48/59	2.4 1.5-3.6	1.013 1.005-1.021	1.060 1.033-1.089
Oligodendroglioma (n=102)								
Wireless phone	55/1052	1.4 0.9-2.2	4/117	0.9 0.3-2.7	7/98	1.8 0.8-4.4	1.008 0.997-1.019	1.044 0.992-1.098
Mobile phone	47/879	1.4 0.9-2.3	1/51	0.6 0.1-4.7	5/33	3.8 1.3-11	1.018 1.001-1.036	1.060 1.002-1.120
Cordless phone	32/643	1.3 0.8-2.2	3/60	1.3 0.4-4.3	3/59	1.3 0.4-4.3	0.990 0.959-1.023	1.011 0.940-1.088
Other/mixed glioma (n=94)								
Wireless phone	42/1052	1.0 0.6-1.6	3/117	0.6 0.2-2.0	6/98	1.3 0.5-3.3	1.007 0.996-1.019	1.009 0.954-1.068
Mobile phone	34/879	0.9 0.5-1.5	1/51	0.5 0.1-3.6	2/33	1.1 0.2-5.1	1.009 0.983-1.035	1.015 0.952-1.082
Cordless phone	25/643	0.9 0.5-1.6	2/60	0.8 0.2-3.4	4/59	1.4 0.5-4.1	1.010 0.995-1.025	0.966 0.891-1.047
Other malignant (n=103)								
Wireless phone	45/1052	1.0 0.6-1.6	5/117	0.9 0.4-2.5	7/98	1.3 0.5-3.0	0.999 0.984-1.014	1.032 0.982-1.085
Mobile phone	39/879	1.0 0.6-1.6	3/51	1.4 0.4-4.8	3/33	1.2 0.3-4.4	1.005 0.980-1.030	1.041 0.985-1.100
Cordless phone	23/643	0.9 0.5-1.5	3/60	1.1 0.3-3.9	4/59	1.2 0.4-3.7	0.994 0.969-1.019	0.987 0.916-1.064

[a]Numbers of exposed cases (Ca) and controls (Co) are given for cumulative life time use in hours. Adjustment was made for age, gender, SEI-code, year of diagnosis and vital status.

Table IV. Odds ratio (OR) and 95% confidence interval (CI) for glioma and astrocytoma and use of different combinations of wireless phones.[a]

	>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
Glioma (n=1148)								
Both mobile and cordless	52/153	0.9	118/213	1.4	91/92	2.2	261/458	1.4
phone		0.6-1.3		1.05-1.8		1.6-3.1		1.1-1.7
Mobile phone only	142/328	1.2	76/135	1.4	50/42	2.6	268/505	1.3
		0.9-1.5		0.98-1.9		1.7-4.1		1.1-1.6
Cordless phone only	77/216	1.0	55/73	1.9	9/15	1.2	141/304	1.3
		0.8-1.4		1.3-2.9		0.5-2.9		0.99-1.6
Astrocytoma (n=952)								
Both mobile and cordless	39/153	0.9	95/213	1.5	85/92	2.6	219/458	1.5
phone		0.6-1.4		1.1-2.0		1.8-3.8		1.2-1.9
Mobile phone only	115/328	1.2	64/135	1.4	41/42	2.6	220/505	1.4
		0.9-1.6		1.01-2.0		1.6-4.2		1.1-1.7
Cordless phone only	54/216	0.9	53/73	2.4	7/15	1.0	114/304	1.3
		0.7-1.3		1.6-3.5		0.4-2.6		0.99-1.7

[a]Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis and vital status. 'Both mobile and cordless phone' denotes that both phone types were used.

although based on few cases. No statistically significantly increased risk was found for cordless phone. Regarding other or mixed glioma (n=94) no statistically significantly increased risk was found (data not in table).

No clear pattern of an association was found for other malignant brain tumours (n=103) either for mobile or cordless phone (data not in table). Use of mobile phone gave an increased risk in the >10 year latency group with OR = 2.7, 95% CI = 1.2-5.8 (n=11 cases, 106 controls), but there was no dose-response relationship. These results were based on low numbers of exposed cases, however.

In Table III results are displayed for three categories of cumulative use in hours of wireless phones. Highest ORs were calculated for astrocytoma with statistically significantly increased risk for mobile phone use in all categories of cumulative number of hours. Regarding cordless phone statistically significantly increased ORs were found in the groups of 1001-2000 h and >2000 h cumulative use. For oligodendroglioma OR = 3.8, 95% CI = 1.3-11 was calculated for use >2000 h of a mobile phone. No statistically significantly increased risks were found for other or mixed glioma, or other malignant brain tumours.

Cumulative use per 100 h of both mobile and cordless phone increased OR statistically significantly for both glioma in total and astrocytoma (Table III). For oligodendroglioma a statistically significantly increased risk was found per 100 h of cumulative use of mobile phone. OR increased statistically significantly per year of latency for use of mobile and cordless phone for glioma and astrocytoma, and for mobile phone and oligodendroglioma.

Results for use of different types or combinations of wireless phones are shown in Table IV. The results were similar for glioma and the subgroup consisting of astrocytoma. Regarding astrocytoma use of mobile phone only, yielded statistically significantly increased risk both for >5-10-year latency and >10-year latency, highest in the latter group with OR = 2.6, 95% CI = 1.6-4.2. For only use of cordless phone OR = 2.4, 95% CI = 1.6-3.5 was calculated in the >5-10-year latency group. Few subjects had used only a cordless phone >10 years.

We present in Table V results for all malignant brain tumours and astrocytoma for first use of the wireless phone in different age groups. Consistently highest risk was found for subjects who started use of a wireless phone before the age of 20 years. Thus, for astrocytoma mobile phone use yielded OR = 4.9, 95% CI = 2.2-11 and cordless phone use yielded OR = 3.9, 95% CI = 1.7-8.7.

Discussion

The results in these analyses were similar as those we have previously reported for malignant brain tumours diagnosed during 1997-2003 (6), where only living cases and controls were included. It has been claimed that excluding deceased cases would bias the results (10). However, in our case-control study on the cases with a malignant brain tumours that had died, using deceased controls and interviewing relatives, we clearly found an increased risk associated with use of mobile phone (11). No statistically significantly increased risk was found for cordless phone, although increased risk was seen in the highest exposure group. These results indicated that

Table V. Odds ratio (OR) and 95% confidence interval (CI) for all malignant brain tumours and astrocytoma in different age groups for first use of the wireless phone.[a]

	All malignant (n=1251)		Astrocytoma (n=952)	
	Ca/Co	OR, CI	Ca/Co	OR, CI
Wireless phone	727/1267	1.3 1.1-1.5	553/1267	1.3 1.1-1.6
<20 years old	28/27	2.1 1.1-3.8	22/27	3.6 1.9-6.9
20-49 years old	415/746	1.2 1.02-1.5	293/746	1.4 1.1-1.7
≥50 years old	284/494	1.3 1.1-1.5	238/494	1.3 1.1-1.6
Mobile phone	574/963	1.3 1.1-1.5	439/963	1.4 1.2-1.7
<20 years old	19/14	2.9 1.3-6.0	15/14	4.9 2.2-11
20-49 years old	347/581	1.3 1.1-1.6	249/581	1.5 1.2-1.9
≥50 years old	208/368	1.2 0.998-1.5	175/368	1.3 1.02-1.6
Cordless phone	432/762	1.3 1.1-1.5	333/762	1.4 1.1-1.7
<20 years old	18/16	2.2 1.1-4.7	14/16	3.9 1.7-8.7
20-49 years old	223/437	1.1 0.9-1.4	157/437	1.3 0.96-1.6
≥50 years old	191/309	1.4 1.1-1.7	162/309	1.4 1.1-1.8

[a]Numbers of exposed cases (Ca) and controls (Co) are given. Adjustment was made for age, gender, SEI-code, year of diagnosis and vital status.

exclusion of deceased cases had not biased our previous results (6).

The rationale for the present study was to include all cases, both living and deceased, with a malignant brain tumour in our previous study. Thus, the results were based on a larger number of cases making subgroup analysis possible. The participation rate was high for both cases and controls, which reduced the risk that selection bias might have influenced the results. Also there were now more long-term users of wireless phones.

One disadvantage was that inclusion of deceased cases and controls might have given less reliable results. However, the published results are similar for this group (11) as for living subjects (6). Furthermore, assessment of the ear mostly used during use of a mobile or a cordless phone was not included in the questionnaire that was sent to the relatives. It was judged that it would be difficult for relatives to answer that question. The other questions on use of wireless phones were the same as for living subjects.

The controls were frequency matched to all cases. Cases with benign tumours were not included in this analysis. The most common benign tumour is meningioma, a disease that occurs more among women than men. All controls for living cases were included and we adjusted for gender since the prevalence of use of wireless phones differs among men and women (Table I). The use is also age-dependent, more common among young persons, so we adjusted for age as a continuous variable. All cases were diagnosed during 1997-2003 and the corresponding control was assigned the same year as the case as cut-off in all assessment of exposure. As can be seen in Table I the distribution of cases and controls was equal over the years.

There has been an increasing prevalence of use of both mobile and cordless phones over the years, so we adjusted for reference date for the cases and controls. Social class has been reported to be a determinant for brain tumours so we adjusted for SEI-code (15). Finally we also adjusted for vital status since assessment of exposure differed for living and deceased subjects. Interestingly the differences for use of wireless phones according to these factors (Table I) were similar among cases and controls.

The main result of this study was an increased risk for malignant brain tumours and use of both mobile and cordless phones. The risk increased with latency period and was highest in the group with >10 years from first use until diagnosis. The finding was consistent both for glioma and astrocytoma, the latter constituting the largest part of glioma. Regarding oligodendroglioma use of mobile phone with >10 year latency and cumulative use >74 h yielded a statistically significantly increased risk. No increased risk was found for other and mixed glioma. A statistically significantly increased risk was found in the group of other malignant brain tumours for use of mobile phone >10 years, but these results were based on low numbers and no dose-response relationship was found. It should be noted that no analysis was performed on laterality of phone use and tumour localisation. Consistently we have found higher risk for ipsilateral use of a wireless phone (6,7). We judged that assessment of laterality of phone use would be less reliable using second hand information from relatives. Nevertheless the overall increased risk would even be higher for ipsilateral use based on our previous findings.

Cumulative use divided into two categories was based on median number of hours among controls. This was rather low, i.e., 74 h for mobile phone use and 243 h for cordless phone use. It is explained by the fact that the study included the time period 1997-2003 for diagnosis and reflects early use of wireless phones. The large increase has been since late 1990s and during the last decade. We also divided cumulative life time use in three categories, similar to our previous publications. Regarding glioma and astrocytoma statistically significantly increased risk was found in all three categories for mobile phone use (Table III), highest OR in the most exposed group (P for trend=0.0001 for glioma, P<0.0001 for astrocytoma). As for use of cordless phone similar results were found in the two highest categories of cumulative use; 1001-

2000 h and >2000 h (P for trend=0.0007 for glioma, P for trend=0.0002 for astrocytoma). We calculated also OR per 100 h cumulative use and per year of latency and similar results as overall for the different tumour types were found (Table III).

In one analysis we calculated the risk for use of only a mobile phone or only a cordless phone. Statistically significantly increased risk was found for use of mobile phone only, for both glioma and astrocytoma (Table IV). For use of cordless phone only, OR was statistically significantly increased in the >5-10 year latency group for both glioma and astrocytoma. It should be noted that the >10 year latency group included very few cases, so the results in that group are less reliable. These results are important since they show that use of mobile phones and cordless phones are independent risk factors for glioma and astrocytoma.

OR was highest both for all malignant brain tumours and astrocytoma for cases that had first used a wireless phone before the age of 20. Thus, mobile phone use yielded OR = 4.9, 95% CI = 2.2-11 and cordless phone OR = 3.9, 95% CI = 1.7-8.7 for astrocytoma. These results are similar as those we have previously reported for astrocytoma cases that were alive (7). It should be noted that in that study the risk was even higher for ipsilateral exposure, for mobile phone OR = 7.8, 95% CI = 2.2-28, cordless phone OR = 7.9, 95% CI = 2.5-25. Of interest is a recent study that showed that the brain is developing until the age of about 20 years (16). The results in the present study were based on low numbers but indicate that young persons may be more susceptible to radiofrequency emissions from wireless phones than older persons. Not the least due to the high prevalence of mobile and cordless phone use among young persons (17,18) our results need to be taken seriously and confirmed or refuted in further studies.

Several overviews and meta-analyses have concluded that there is a consistent pattern of an association between long-term mobile phone use and glioma (5,7,19,20). However, no other studies than from our research group have assessed use of cordless phones. As we have discussed elsewhere (6) exposure from use of cordless phone is equal or even higher than that from a GSM phone since the latter regulates the output power depending on the quality of transmission (3). Furthermore, cordless phones are used for longer calls than mobile phones as also shown in our tables (higher median cut-off). Thus, not taking inte account use of cordless phones would bias the risk towards unity.

There are scanty data on long-term use, >10 years, of wireless phones besides our studies. Results from the Interphone study group have been published for glioma and meningioma (21). For glioma OR = 1.40, 95% CI = 1.03-1.89, was calculated in the group with highest cumulative use of mobile phone, ≥1640 h. For ipsilateral use, the risk increased further to OR = 1.96, 95% CI = 1.22-3.16. Highest risk was found in the temporal lobe, the anatomical area with highest exposure. Overall statistically significantly decreased risk was found both for meningioma and glioma indicating bias in the study as also discussed by the authors. Consequently the OR was biased towards unity in the highest exposure group. Using the lowest exposure group as reference entity yielded for glioma and latency ≥10 years OR = 2.18, 95% CI = 1.43-3.31 and for cumulative use ≥1640 h OR = 1.82, 95% CI = 1.15-2.89.

These results are thus consistent with our findings and give further evidence of an association between mobile phone use and glioma. However, use of cordless phones was not assessed in the Interphone study, such exposure was included in the 'unexposed group'. This indicates that the published ORs would be lower than expected if use of cordless phones had been included in the exposed group (22).

In conclusion our pooled analysis showed an increased risk for malignant brain tumours and use of mobile or cordless phones. The risk increased with latency time and cumulative use. Highest risk was found in the group with first use of a wireless phone before 20 years of age.

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