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Mobile phone use and risk of glioma in 5 North European countries

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Public concern has been expressed about the possible adverse health effects of mobile telephones, mainly related to intracranial tumors. We conducted a population-based case–control study to investigate the relationship between mobile phone use and risk of glioma among 1,521 glioma patients and 3,301 controls. We found no evidence of increased risk of glioma related to regular mobile phone use (odds ratio, OR = 0.78, 95% confidence interval, CI: 0.68, 0.91). No significant association was found across categories with duration of use, years since first use, cumulative number of calls or cumulative hours of use. When the linear trend was examined, the OR for cumulative hours of mobile phone use was 1.006 (1.002, 1.010) per 100 hr, but no such relationship was found for the years of use or the number of calls. We found no increased risks when analogue and digital phones were analyzed separately. For more than 10 years of mobile phone use reported on the side of the head where the tumor was located, an increased OR of borderline statistical significance (OR = 1.39, 95% CI 1.01, 1.92, *p* trend 0.04) was found, whereas similar use on the opposite side of the head resulted in an OR of 0.98 (95% CI 0.71, 1.37). Although our results overall do not indicate an increased risk of glioma in relation to mobile phone use, the possible risk in the most heavily exposed part of the brain with long-term use needs to be explored further before firm conclusions can be drawn.

Key words: mobile phones; brain tumors; case–control studies

Mobile phone use has increased rapidly worldwide since the early 1990s. Mobile phones emit radiofrequency electromagnetic fields that are non-ionizing radiation, *i.e.* have too low energy to break chemical bonds. Hence, such fields cannot cause DNA damage (mutations), which is required for cancer initiation.[1] However, radiofrequency fields might be involved in cancer development at later stages, including tumor progression or promotion. Despite the fact that no carcinogenic mechanism for radiofrequency radiation has been established,[2] there is public concern about the possible health effects of mobile phone use. This is mainly related to intracranial tumors, as mobile phones are used close to the head and the radiofrequency field is absorbed mostly in the head and neck region. The studies published on the issue have covered a relatively small number of study subjects with long-term exposure, and so far the epidemiological evidence does not suggest any clear increase of intracranial tumors related to mobile phone use, although some positive findings have been reported.[3–19]

We conducted a collaborative population-based case–control study on the association of mobile phone use with intracranial tumors in 5 Northern European countries, using a shared protocol of the INTERPHONE study coordinated by the International Agency for Research on Cancer.[20] We report here the results concerning glioma, based on the combined data from Denmark, Finland, Norway, Sweden and Southeast England, where mobile phones have been widely used for at least a decade.[21]

Materials and methods

Study design and population

This population-based case–control study on mobile phone use and risk of gliomas was conducted in Denmark (nationwide), Finland (98% of the population, excluding Northern Lapland and Åland), Norway (the Southern and Middle parts), Sweden (geographical areas covered by the regional Cancer Registries in Umeå, Stockholm, Gothenburg and Lund regions) and the United Kingdom (Thames region of Southeast England). Of these, the Swedish, Danish and British studies have been reported previously.[11,12,15] We recently reported also a collaborative analysis of acoustic neuromas based on these studies.[13]

Eligible cases were subjects resident in the study areas and diagnosed with glioma (International Classification of Diseases for Oncology, Third Edition, codes 9380–9384, 9390–9394, 9400, 9401, 9410, 9411, 9420–9424, 9430, 9440–9444, 9450–9451, 9505) between September 2000 and February 2004 (the study periods were different between countries) at ages 20–69 years in the Nordic countries and 18–59 years in Southeast England. The material reported here is based on a wider age range than that in the INTERPHONE Study[20] to increase the number of study subjects and to cover the young age groups with intensive mobile phone use. Incident cases were identified through neurosurgery, oncology and neurology departments in the study areas. Cases were also checked against the national or regional cancer registries to evaluate and enhance completeness of coverage.

In the Nordic countries, controls were selected from national population registers with frequency-matching on age, sex and region of residence of cases. In the UK, where no such population register exists, the controls were randomly selected from general practitioners' lists, frequency-matched on the above-mentioned factors. Cases were approached either by mail, or personally at the clinics with written information about the study, and were requested to participate in the study, whereas all controls were approached by mail. If there was no reply from those who were approached by mail, another letter was sent or the subject was approached by telephone. All study subjects received both an invitation letter and written information about the study before asking for participation. The study protocols in each country were approved by the local ethics committees. Informed consent was obtained from all study subjects.

Data collection

Trained interviewers conducted the personal interviews. Typically, the interviews were performed at hospital or at the subject's home; with 11% of interview of cases and 6% for controls conducted over the telephone (mainly in Norway). The interview was computer-

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assisted in all countries, except Finland where a paper questionnaire with identical wording was used. In the interview, information was obtained on the use of handheld mobile phones, medical history, highest level of education attained and family history of brain tumors. The DECT phones or other cordless phones were not enquired about because they were not regarded as potential material exposure sources, since the average power that they transmit is only 0.01 W *vs* 0.25/0.125 W with GSM 900/1800 phones. Regular use of mobile phones (at least once a week for at least 6 months) was assessed. For regular users, the interview covered a detailed history of mobile phone use, including start and end dates of use, types of phones used and the frequency of use, laterality, use of hands-free equipment, and other circumstances of use such as type of telephone network. Show cards either on paper or on the computer were used in all countries to aid participants' recall of the models of phones they had regularly used. Information on the model of phones, calendar period of use, operator and network code of the phone number was used to classify phones as analogue and digital.

Statistical analysis

Three intracranial tumor types (glioma, meningioma and acoustic neuroma) were included in the INTERPHONE study. Since frequency-matching was used throughout the study, we have used the entire control group for all intracranial tumors in the frequency matching strata of the glioma cases, in order to maximize power.

Based on the information obtained in the interview, several characteristics related to mobile phone use were investigated, including ever and regular mobile phone use, the cumulative number of calls, the cumulative hours of mobile phone use, lifetime years of use and years since first use. Continuous exposure variables were classified into categories with the cut-points based on the distribution among controls; the never and non-regular users formed the reference category with the median and third quartile of the exposure variable among regular mobile phone users used as the other cut-points. In addition, the highest exposure group was investigated in some analyses, with the cut-point defined as the highest 10% of controls with regular mobile phone use. The cumulative number of calls and the cumulative hours of mobile phone use were adjusted for the reported use of hands-free devices, using methods described previously.[9,10]

All exposure within 1 year before the reference date was ignored, except when calculating the years since first use of mobile phones (Table III). For cases, the reference date was the date of diagnosis, *i.e.* $\text{refdate}_{\text{case}} = \text{diagdate}_{\text{case}}$. For controls, the reference date was set based on the interview date of the control, with adjustment for the mean interval between the diagnostic and interview date of cases and the difference between the mean interview date of cases and controls, *i.e.* $\text{refdate}_{\text{control}} = \text{intdate}_{\text{control}} - (\text{mean intdate}_{\text{cases}} - \text{mean diagdate}_{\text{cases}}) - (\text{mean intdate}_{\text{cases}} - \text{mean intdate}_{\text{controls}})$. This correction was made to adjust for the fact that the controls were interviewed on average later than the cases, and because the prevalence of mobile phone use increased rapidly with calendar period.

The odds ratios (OR) for glioma risk in relation to mobile phone use were obtained by using conditional logistic regression, with strata defined by country, region, sex and five-year age group at the reference date. Educational level, family history of glioma, previous radiation therapy to the head and neck region (received more than 10 years before the reference date), neurofibromatosis or tuberous sclerosis of the subject were regarded as potential confounders. All the analyses were conducted both with and without taking into account the effects of potential confounding factors (by adjustment for education and family history of glioma, and additionally, excluding subjects with a history of radiotherapy to the head and neck or with hereditary conditions affecting the risk of glioma). The results were not materially affected by taking into account those potential confounding factors, in all instances the effect was less than 2%, and therefore the stratified estimates without adjustment for potential confounders (other than those used for matching) are reported. The statistical significance of trend in risk of glioma in relation to exposure was obtained by using a linear term, which was assigned values corresponding to the ordered exposure categories (*e.g.* 4 exposure classes numbered 1–4). This was done both for the entire study population with subjects not using mobile phones regularly as baseline and also separately with exclusion of the nonexposed subjects.

ORs were obtained by type of phone (analogue and digital) and also separately for glioblastomas (ICD-O-3 codes 9440, 9441, and 9442), representing the largest subgroup of gliomas. The ORs for regular mobile phone use were also calculated separately for men and women and by 5-year age group at the reference date. Laterality analyses, where the location of the tumor was assessed in relation to the reported predominant side of mobile phone use, were also conducted based on 2 previously described methods.[5,10] The reliability of the latter method[10] was also investigated by simulations, repeating the random allocation of index hemisphere (corresponding to tumor laterality) to controls 500 times independently. Further, analyses were conducted both based on the whole dataset and individually by country. Heterogeneity in the results between countries, 5-year age groups and sexes were assessed with a log likelihood ratio test by comparing nested models with one including both main effects and an interaction between the factor, for instance the country, and the exposure and the other including only the main effects. The statistical software STATA (version 9) was used for all the analyses.[22]

Results

A total of 2,530 potential cases and 6,581 potential controls were invited to participate in the study. Of the eligible cases, 60% (1,521 subjects) participated (range 37–81% between countries, Table I). The corresponding figure for controls was 50% (3,301

TABLE I – COUNTRY SPECIFIC DETAILS OF THE CASES AND CONTROLS

	Denmark	Finland	Norway	Sweden	UK-Southeast England	Total
Cases						
Included	247	266	284	363	361	1,521
Participation rate	71%	81%	77%	74%	37%	60%
Number with histopathology	247	262	274	339	344	1,466
Interview lag, median and interquartile range (days)	68 (39–115)	15 (3–31)	452 (192–732)	87 (55–146)	142 (39–244)	92 (39–244)
Interview type						
Hospital	120	264	56	210	12	662
Home	117	0	64	92	329	602
Other/missing	10	2	164	61	20	257
Telephone	0	3	145	18	0	166
Controls						
Included	819	870	353	629	630	3,301
Participation rate	52%	42%	69%	66%	43%	50%
Number of telephone interviews	0	7	159	40	2	208

TABLE II – DEMOGRAPHIC CHARACTERISTICS OF THE STUDY POPULATION

	Cases (n = 1,521)		Controls (n = 3,301)	
	N	%	*N*	%
Sex				
Male	893	58.7	1,530	46.4
Female	628	41.3	1,771	53.7
Age at reference date (years)				
18–29	145	9.5	245	7.4
30–39	265	17.4	486	14.7
40–49	323	21.2	761	23.1
50–59	484	31.8	1,097	33.2
60–69	304	20.0	712	21.6
Highest educational level				
Compulsory school	429	28.2	933	28.3
Secondary/vocational school	367	24.1	789	23.9
Upper secondary school	336	22.1	832	25.2
University	380	25.0	740	22.4
Not known	9	0.6	7	0.2
Country				
Denmark	247	16.2	819	24.8
Finland	266	17.5	870	26.4
Norway	284	18.7	353	10.7
Sweden	363	23.9	629	19.1
Southeast England	361	23.7	630	19.1

subjects, range 42–69%). The main reasons for nonparticipation were refusal (8% of cases and 33% of controls), illness or death (18% of cases and 0.5% of controls) and inability to contact the subject (7% of cases and 15% of controls). Proxy interviews were used for 12% of cases and <1% of controls. The quality of the information received in the interview was evaluated by the interviewers and 67% of cases and 78% of controls were judged by the interviewer to recall their mobile phone use "well" or "very well." Demographic characteristics of the study subjects are shown in Table II.

Ever use of a mobile phone was reported by 92% (1,389) of cases and 94% (2,945) of controls. The OR for glioma in relation to ever use of a mobile phone was 0.63 (95% confidence interval, CI, 0.48, 0.82). Of the cases, 58% (867) reported using a mobile phone regularly while the figure for regular use by controls was 59% (1,853). For regular mobile phone use, the OR was 0.78 (0.68, 0.91) (Table III). The country-specific results for regular use were 0.70 (0.51, 0.96) for Denmark, 0.80 (0.56, 1.13) for Finland, 0.62 (0.42, 0.91) for Norway, 0.82 (0.61, 1.09) for Sweden and 0.95 (0.70, 1.29) for Southeast England. There was no significant heterogeneity between countries in results for regular use (p = 0.47) or any other indicator of mobile phone use (results not shown).

TABLE III – ODDS RATIOS OF GLIOMA (INCLUDING GLIOBLASTOMA) AND GLIOBLASTOMA SEPARATELY RELATED TO MOBILE PHONE USE, WITH NUMBER OF CASES AND CONTROLS INCLUDED IN THE ANALYSES

	All glioma (n = 1,521)	OR (95% CI)	Glioblastoma (n = 710)	OR (95% CI)	Controls (n = 3,301)
Frequency of use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
Regular use	867	0.78 (0.68, 0.91)	368	0.77 (0.64, 0.93)	1,853
Years since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
1.5–4[2]	384	0.77 (0.65, 0.92)	165	0.82 (0.65, 1.04)	895
5–9	342	0.75 (0.62, 0.90)	141	0.69 (0.54, 0.88)	739
≥10	143	0.95 (0.74, 1.23)	64	0.86 (0.62, 1.21)	220
		p for trend = 0.28		p for trend = 0.08	
		p trend, for users only = 0.29		p trend, for users only = 0.93	
Lifetime years of use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
0.5–4	504	0.75 (0.64, 0.88)	210	0.77 (0.62, 0.96)	1,176
5–9	259	0.78 (0.64, 0.95)	111	0.73 (0.56, 0.96)	529
≥10	88	0.94 (0.69, 1.28)	38	0.77 (0.51, 1.17)	134
		p for trend = 0.67		p for trend = 0.14	
		p trend, for users only = 0.27		p trend, for users only = 0.81	
Cumulative number of calls[1,3]					
Never/nonregular use	626	1.0	327	1.0	1,278
<2,172	352	0.73 (0.62, 0.87)	153	0.71 (0.56, 0.89)	897
2,172–7,792	205	0.74 (0.60, 0.91)	87	0.79 (0.59, 1.05)	444
>7,792	265	0.91 (0.74, 1.12)	104	0.83 (0.63, 1.11)	455
		p for trend = 0.93		p for trend = 0.49	
		p trend, for users only = 0.05		p trend, for users only = 0.24	
Cumulative hours of use [1,3]					
Never/nonregular use	626	1.0	327	1.0	1,278
<125	368	0.75 (0.64, 0.89)	166	0.75 (0.60, 0.95)	895
125–503	193	0.69 (0.55, 0.85)	79	0.66 (0.49, 0.89)	446
>503	262	0.90 (0.73, 1.10)	100	0.85 (0.63, 1.13)	455
		p for trend = 0.98		p for trend = 0.50	
		p trend, for users only = 0.09		p trend, for users only = 0.30	
Cumulative number of calls by time since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
<10 years	724	0.76 (0.65, 0.88)	304	0.75 (0.62, 0.92)	1,633
≥10 years (≤1,512 calls)	49	0.68 (0.47, 0.99)	25	0.67 (0.41, 1.08)	111
≥10 years (>1,512 calls)	83	1.12 (0.81, 1.55)	31	0.89 (0.57, 1.41)	106
Cumulative hours of use by time since first use[1]					
Never/nonregular use	629	1.0	330	1.0	1,281
<10 years	724	0.76 (0.65, 0.88)	304	0.75 (0.61, 0.92)	1,633
≥10 years (≤75 h)	52	0.70 (0.48, 1.01)	25	0.66 (0.41, 1.07)	111
≥10 years (>75 h)	81	1.13 (0.82, 1.57)	32	0.93 (0.59, 1.46)	105

[1]The numbers do not match exactly to the total numbers of cases (1,521) and controls (3,301) since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]Lower limit 1.5 years since phone use was defined as regular when phone was used at least 6 months at least 1-year before reference date.–[3]Estimates adjusted for use of hands-free devices.

TABLE IV – ODDS RATIOS FOR GLIOMA IN RELATION TO ANALOGUE AND DIGITAL MOBILE PHONE USE

	Analogue			Digital		
	Cases[1]	Controls[1]	OR (95% CI)	Cases[1]	Controls[1]	OR (95% CI)
Frequency of use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
Regular use	232	471	0.85 (0.68, 1.06)	788	1,750	0.75 (0.65, 0.87)
Years since first use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
1.5–4[3]	26	55	1.22 (0.72, 2.08)	458	1,091	0.72 (0.61, 0.85)
5–9	99	233	0.70 (0.52, 0.95)	326	648	0.80 (0.66, 0.96)
≥10	108	187	0.93 (0.69, 1.25)	4	12	0.53 (0.16, 1.72)
			p for trend = 0.26			p for trend = 0.04
			p trend, for users only = 0.71			p trend, for users only = 0.37
Lifetime years of use						
Never/nonregular use[2]	629	1,281	1.0	629	1,281	1.0
0.5–4	156	313	0.90 (0.69, 1.16)	587	1,372	0.72 (0.62, 0.85)
5–9	59	125	0.75 (0.51, 1.08)	198	374	0.83 (0.67, 1.04)
≥10	16	31	0.92 (0.48, 1.77)	0	0	Not available
			p for trend = 0.27			p for trend = 0.64
			p trend, for users only = 0.67			p trend, for users only = 0.20
Cumulative number of calls[4]						
Never/nonregular use[2]	629	1,281	1.0	626	1,278	1.0
<Median	111	231	0.88 (0.67, 1.17)	337	846	0.73 (0.61, 0.87)
Median-3rd quartile	47	117	0.61 (0.41, 0.90)	178	418	0.68 (0.54, 0.85)
>3rd quartile	64	112	1.01 (0.69, 1.46)	237	425	0.86 (0.70, 1.07)
			p for trend = 0.68			p for trend = 0.52
			p trend, for users only = 0.43			p trend, for users only = 0.18
Cumulative hours of use[4]						
Never/nonregular use[2]	629	1,281	1.0	704	1,377	1.0
<Median	114	232	0.92 (0.70, 1.22)	335	843	0.72 (0.60, 0.86)
Median-3rd quartile	45	116	0.51 (0.34, 0.77)	173	419	0.68 (0.54, 0.84)
>3rd quartile	64	114	1.04 (0.71, 1.52)	243	427	0.87 (0.71, 1.08)
			p for trend = 0.82			p for trend = 0.75
			p trend, for users only = 0.72			p trend, for users only = 0.08

[1]The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]The reference category consists of subjects with never/nonregular use of any type of phone.–[3]Lower limit 1.5 years since phone use was defined as regular when the phone was used at least 6 months during the period at least 1-year before the reference date.–[4]Estimates adjusted for use of hands-free devices. For cumulative number of calls the data are divided, based on the distribution in controls, into <2,920, 2,920–8,583 and >8,583 for analogue phones, and <1,829, 1,829–6,019 and >6,019 for digital phones. For cumulative hours of mobile phone use the data are divided into <147, 147–492 and > 492 for analogue phones, and <102, 102–394 and >394 for digital phones.

Years since first use and lifetime years of mobile phone use both gave an OR of 0.99 (0.97, 1.01) per year (p for trend 0.28 for years since first use and 0.67 for lifetime years of use). When we restricted the analysis to regular mobile phone users, the results remained largely similar (trend test p-values 0.29 and 0.27 for years since first use and lifetime years of mobile phone use, respectively). There was no increased risk for greater cumulative number of calls (OR = 1.00 per 10,000 calls, 95% CI: 0.97, 1.04, adjusted for hands-free devices). For cumulative hours of mobile phone use, the OR was 1.006 per 100 hr (1.002, 1.010, adjusted for hands-free devices) when such use was analyzed as a continuous variable, but there was no trend of risk with cumulative hours of use when the data were examined in categories (Table III). The subgroup with the highest cumulative call hours (>1475 hr, the cut-point defined as the highest 10% of controls with regular mobile phone use), had a slightly increased but non-significant OR (1.13, 95% CI: 0.86, 1.48) whereas that with the highest cumulative number of calls (>21,740 calls) showed no increased risk (OR = 0.95, 95% CI 0.72, 1.26). The cumulative number of calls 10 years or more before the reference date was not associated with a significantly increased risk of glioma (OR = 1.09 per 10,000 calls, 95% CI: 0.89, 1.35; p for linear trend 0.14). Further, for cumulative hours of mobile phone use more than 10 years before the reference date, the OR was 1.03 per 100 hr (1.00, 1.05; p for trend 0.16).

When we performed the analyses separately for glioblastoma, we found no statistically significantly increased risk in relation to mobile phone use in any analysis. The results for glioblastoma did not differ substantially from the results for all gliomas (Table III).

There was no evidence of increased risk of glioma related to regular use of analogue or digital telephones (OR for analogue telephones = 0.85, 95% CI: 0.68, 1.06, for digital telephones 0.75, 95% CI: 0.65, 0.87, Table IV). From the analyses of continuous variables, the OR for years since first use for analogue telephones (mean 9.2 years among regular users) was 0.99 (0.97, 1.01) per year, whereas for digital telephones (mean 4.6 years among regular users), the OR was 0.97 (0.95, 1.00) per year.

Similar results were obtained for men and women: the OR for regular use was 0.79 (0.65, 0.96) for men and 0.78 (0.63, 0.96) for women (p for heterogeneity between sexes 0.94). In the analysis of regular use by 5-year age group, no systematic differences were found by age at reference date; the OR was smallest for the second youngest age group (25–29 years) (0.33, 95% CI: 0.16, 0.69; p for heterogeneity between age groups 0.39). No significant heterogeneity between age groups or sexes was found for any other exposure characteristic (*i.e.* ever use, cumulative number of calls, cumulative hours of use and regular ipsilateral use) either. No differences in results were found related to a histopathological confirmation of diagnosis (available versus not) and interview type (hospital/home/telephone).

The OR for regular ipsilateral use of mobile phones (phone use reported to be on the same side of the head as the tumor was located), based on assigning an index hemisphere randomly to controls,[10] was 1.13 (0.97, 1.31), whereas the OR for regular contralateral use (phone use on the opposite side of the head to the tumor) was 0.75 (0.64, 0.88) (Table V). The ORs for first ipsilateral and contralateral use 10 or more years ago were 1.39 (1.01, 1.92, p trend for duration of ipsilateral use 0.04) and 0.98 (0.71, 1.37, p trend for duration of contralateral use 0.11), respectively, based on the same method (Table V). Excluding the subjects who had used mobile phone on both sides of the head from the analyses did not

TABLE V – ODDS RATIOS FOR GLIOMA RELATED TO LATERALITY OF THE TUMOR AND REPORTED SIDE OF MOBILE PHONE USE

	Ipsilateral exposure[1]			Contralateral exposure[1]		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Frequency of use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
Regular	471	1,002	1.13 (0.97, 1.31)	354	986	0.75 (0.64, 0.88)
Years since first use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
1.5–4[3]	205	485	1.08 (0.88, 1.31)	150	474	0.70 (0.57, 0.87)
5–9	189	400	1.10 (0.89, 1.35)	137	391	0.74 (0.59, 0.92)
≥10	77	117	1.39 (1.01, 1.92)	67	121	0.98 (0.71, 1.37)
			p for trend = 0.04			p for trend = 0.11
			p trend, for users only = 0.18			p trend, for users only = 0.20
Lifetime years of use						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
0.5–4	275	639	1.07 (0.90, 1.28)	199	625	0.70 (0.58, 0.85)
5–9	144	282	1.18 (0.93, 1.49)	109	280	0.79 (0.61, 1.01)
≥10	43	74	1.14 (0.76, 1.72)	41	71	1.01 (0.67, 1.53)
			p for trend = 0.21			p for trend = 0.45
			p trend, for users only = 0.40			p trend, for users only = 0.21
Cumulative hours of use[4]						
Reference category[2]	803	2,127	1.0	920	2,143	1.0
<Median	202	492	1.05 (0.86, 1.28)	140	485	0.67 (0.54, 0.83)
Median-3rd quartile	114	251	1.03 (0.80, 1.33)	97	249	0.78 (0.60, 1.02)
>3rd quartile	136	247	1.24 (0.97, 1.59)	106	240	0.85 (0.65, 1.10)
			p for trend = 0.69			p for trend= 0.01
			p trend, for users only = 0.36			p trend, for users only = 0.07

[1]Ipsilateral exposure = mobile phone use on the same side of the head as the tumor. Contralateral exposure = mobile phone use on the opposite side of the head to the tumor. The numbers do not match exactly to the total numbers of cases and controls since there were strata without cases and strata without controls in the data. We report here the numbers of cases and controls that are actually included in the analyses and for whom the values of the explored exposure variables were known.–[2]Reference category is never/nonregular use of mobile phones, and for ipsilaterality, phone use only on the opposite side of the head, and for contralaterality, phone use only on the same side of the head.–[3]Lower limit 1.5 years since phone use was defined as regular when phone was used for at least 6 months during the period at least 1-year before reference date.–[4]Estimates adjusted for use of hands-free devices. Data are divided, based on the distribution in controls, into <136, 136–567 and >567 for ipsilaterality, and <132, 132–553 and >553 for contralaterality.

substantially affect the results (not shown). When restricting the analysis to subjects with the quality of interview related to mobile phone use rated as good or very good by the interviewers, the OR for first ipsilateral use 10 or more years ago was 1.21 (0.74, 1.96). As the laterality analysis method is sensitive to random allocation of the controls, its reliability was investigated. Based on 500 simulations the method seemed rather stable, as the mean of the OR for regular ipsilateral use was 1.12 (range 1.00–1.24) and for regular contralateral use it was 0.76 (range 0.68–0.86).

A case-only analysis gave an overall relative risk (RR) for ipsilateral mobile phone use of 1.24 (Fisher's exact test: $p < 0.001$, two-sided), based on 674 (44%) cases for whom both the side of the tumor and the side of phone use were defined. For the subjects ($n = 60$) with 10 or more years of exposure history (lifetime years of mobile phone use), the ipsilateral RR was 1.01 ($p = 1.00$) whereas for subjects ($n = 106$) for whom the first use of a mobile phone was more than 10 years ago (years since first use), the RR was 1.09 ($p = 0.53$).

Discussion

The results of our analyses do not provide consistent evidence for increased risk of glioma related to use of mobile phones. We did not find indications of increased risk related to regular mobile phone use overall, or in the majority of the subanalyses based on various exposure characteristics. The most exposed group (the highest 10% based on the exposure distribution among controls) did not show an elevated risk of glioma. Neither did the dose-response analyses reveal a clear trend in relation to the overall duration of mobile phone use, number of calls or hours of use. No differences were found between analogue and digital phones and the results for glioblastoma were similar to those including all gliomas. Data from different countries also gave consistent results. One subset of analyses did, however, indicate a possible association with mobile phone use: reported ipsilateral use 10 or more years ago was associated with significantly increased risk of glioma and there was also an increasing trend with years since first use on the ipsilateral side. Analyses of risk in relation to cumulative hours of mobile phone use yielded mixed results and are of very uncertain interpretation because they depend on the analytical method used and they may be driven by a small number of extreme values that may be biased or erroneous. We also note that the results reported here are to a certain degree sensitive to choice of analytical method, and hence are not always identical with those reported in national publications.[11,12,14]

In previous studies, largely negative results have been published.[23] In the German INTERPHONE study, mobile phone use for at least 10 years was associated with an increased glioma risk of borderline significance.[15] In the UK study, with material partly overlapping that in the present analyses, increased risk of ipsilateral use was found, but with a corresponding decrease on the contralateral side.[14] The Danish and Swedish data were published previously and the results did not indicate significantly increased risk of glioma related to mobile phone use.[11,12] Another Swedish group has found increased risks related to several aspects of mobile phone use,[16–19] but the reason for findings inconsistent with most other reports remains unclear. A meta-analysis also failed to reveal any significant association between long-term mobile phone use and intracranial tumors.[24] Most earlier studies[3–8] did not have sufficient numbers of long-term mobile phone users for meaningful risk assessment, if there is a latency of at least 5–10 years.

Our study covers a large number of cases and controls compared with previously published reports: the largest earlier study included less than 1,000 gliomas.[14] Additionally, the countries included in these analyses are pioneers in mobile phone use and therefore the number of mobile phone users with more than 10 years of exposure (88 cases) is larger than in previous analyses, which allows more reliable estimation of the risk related to such long-term mobile phone use. We adjusted exposure history to

match the reference period between cases and controls to account for later interviewing of the controls, which is crucial to ensure comparability of information for a rapidly changing exposure such as mobile phone use. Few risk factors requiring control of potential confounding are known for glioma. We collected information on high-dose radiation, hereditary risk factors and family history. They were, however reported by only few subjects and exclusion of exposed persons did not affect our results. Therefore, the role of confounding appears minimal.

When a frequently fatal condition, such as glioma, is studied, rapid loss of study subjects is inevitable. In the light of this, the participation in our study is fairly high for cases in general. Yet, participation among potential controls was quite low, which can potentially induce selection bias. Previously, mobile phone users have been found more likely to participate than non-users among both cases and controls in Finland and Sweden.[11,25] This may be related to more common use of mobile phone use among people with high level of education and socio-economic status, who are also more willing to participate in research. However, this finding is based on a relatively small number of non-participants who were willing to report their mobile phone use, and may not therefore be directly applicable to the present results. In the current report, the significantly reduced OR for ever *vs*. never use of mobile phones might be explained by this bias, in which case other ORs in the study might have been similarly affected. On the other hand, arguing against this, the country-specific ORs were not associated with the participation rates.

Overestimation of exposure among controls due to selective participation may underestimate true effects, *i.e*. bias results towards the null. In the present study, we performed the trend analyses for years since first use and lifetime years of use also based only on the regular mobile phone users, as such an analysis would be less prone to selection bias if there is more selection between users and non-users than between subjects with different amount of mobile phone use. In both cases, the trend remained fairly unchanged although the point estimate was increased slightly towards unity. This finding is also consistent with the possibility that selection bias may have produced an apparent protective effect of mobile phone use in this study, reflected in the odds ratio below 1 for regular use.

Mobile phone use is nowadays an unremarkable part of everyday activities. Therefore, accurate recall of past patterns may be problematic. Also, the amount of use has tended to increase which may result in reporting exposures reflecting more closely current than past behavior. Reports of past mobile phone use are subject to random error, as recall even in the short term has been shown to be inaccurate.[26–29] Over-reporting of the amount of mobile phone use by 50–100% has been common. This is likely to attenuate any true relationship between exposure and outcome, and it might distort dose-response. However, information on whether the subject used the phone regularly and on year of first use is likely to be more reliable.

Bias due to differential recall of exposure by cases and controls usually tends to overestimate the true effects. Overall, reported regular use of a mobile phone on the same side as that on which the brain tumor was diagnosed (ipsilateral use) was not associated with a significantly increased risk of glioma, when analyzed with the method used by Lönn and coworkers.[10] The risk estimate for ipsilateral use was slightly above unity, while that for contralateral use was below one. This finding could be attributable to recall bias. Yet, the risk seemed to increase with duration of ipsilateral phone use. The method of Inskip also showed a slight increase for tumors located on the same side as the mobile phone was used, although not significantly so for long-term use, based however only on a fifth of the total number of study subjects. The advantage of the case–case analysis is the avoidance of recall bias. These findings leave open the possibility that long-term mobile phone use may increase the risk of gliomas in the more exposed hemisphere.

However, findings related to reported ipsilateral use of mobile phone are difficult to interpret and lend themselves to both causal and non-causal (artefactual) explanations. On one hand, the radiofrequency field is highly local and any possible effect may be limited to a small segment of the brain. On the other hand, there is considerable potential for uncertainty in reporting the side where the mobile phone is held, particularly for exposures a long time ago. This may induce both random error and bias. Recall bias may affect the reported side of mobile phone use if cases overreport use on the side where the tumor was diagnosed, leading to spuriously elevated risks. This would be most likely to occur if mobile phone use was perceived as a potential cause of cancer. Our studies were not introduced to the participants as focusing on mobile phone use (except in Sweden), but nevertheless, most subjects were likely to be aware of this hypothesis due to media coverage of the issue.

Our finding of decreased risk related to regular use on the contralateral side is consistent with recall bias. The interviewers regarded the quality of information slightly better for controls than cases in our study. Restriction of analysis to subjects with the estimated best quality of information related to mobile phone use gave slightly lower, non-significant risk estimates for ipsilateral use, which may indicate information bias. It appears therefore that exposure assessment based on interview may induce errors in both directions, overestimation and underestimation of effects. The only way to avoid these shortcomings is to use more objective sources of information, such as operator records. They were, however, not available for the purposes of this study.

In conclusion, our results do not support mobile phone use for less than 10 years as a cause of glioma. However, we found an indication of increased risk in relation to reported ipsilateral phone use of more than 10 years duration. This may be due to either chance or causal effect or information bias, *i.e*. overreporting of mobile phone use on the affected side by the cases with brain tumors.

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