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ORIGINAL ARTICLE

Mobile phone use and brain tumours in the CERENAT case-control study

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ABSTRACT

The carcinogenic effect of radiofrequency electromagnetic fields in humans remains controversial. However, it has been suggested that they could be involved in the aetiology of some types of brain tumours.

Objectives The objective was to analyse the association between mobile phone exposure and primary central nervous system tumours (gliomas and meningiomas) in adults.

Methods CERENAT is a multicenter case-control study carried out in four areas in France in 2004–2006. Data about mobile phone use were collected through a detailed questionnaire delivered in a face-to-face manner. Conditional logistic regression for matched sets was used to estimate adjusted ORs and 95% CIs.

Results A total of 253 gliomas, 194 meningiomas and 892 matched controls selected from the local electoral rolls were analysed. No association with brain tumours was observed when comparing regular mobile phone users with non-users (OR=1.24; 95% CI 0.86 to 1.77 for gliomas, OR=0.90; 95% CI 0.61 to 1.34 for meningiomas). However, the positive association was statistically significant in the heaviest users when considering life-long cumulative duration (≥896 h, OR=2.89; 95% CI 1.41 to 5.93 for gliomas; OR=2.57; 95% CI 1.02 to 6.44 for meningiomas) and number of calls for gliomas (≥18 360 calls, OR=2.10, 95% CI 1.03 to 4.31). Risks were higher for gliomas, temporal tumours, occupational and urban mobile phone use.

Conclusions These additional data support previous findings concerning a possible association between heavy mobile phone use and brain tumours.

What this paper adds

- The potential association between mobile phone use and brain tumour remains controversial, and original data have mostly been provided by studies performed in Sweden and the international Interphone study.
- Some studies suggest that long-term (over 10 years) mobile phone use increases the risk of gliomas, and especially of those with temporal location.
- This analysis highlights a positive association between heavy use of mobile phone and brain tumour, considering life-long cumulative duration and number of calls.
- Risks were higher for gliomas, temporal tumours, occupational and urban mobile phone use.
- This study provides additional data supporting a possible association between heavy mobile phone use and brain tumours.

INTRODUCTION

The number of mobile phone subscriptions over the last decade has increased ninefold to reach a startling 6 billion users worldwide in 2011, according to the International Telecommunication Union. From the 1980s, mobile phones have evolved over four different generations, and services have developed very fast (text messaging, internet access, etc). These changes have led to a dramatic growth in mobile phone usage. According to the French Telecommunications and Posts Regulator, the individual mean use for calls in France today is 150 min/month (+27% since 2000), excluding other services and specific usages, such as occupational ones.

The potential carcinogenic effects of radiofrequency electromagnetic fields (RF-EMF) remain controversial. In vitro studies have explored various hypotheses including genotoxicity, cell proliferation, apoptosis, gene expression and direct effect on proteins, but there is still no consensus.[1] Owing to direct contact with the head during communications, the potential association between brain tumours and mobile phone use has become a foremost concern.

For 15 years, original data have mostly been provided by case-control studies, including four studies performed in Sweden,[2–6] and the international Interphone study.[7] Only two cohort studies have addressed the issue; one initiated in Denmark in 1982,[8] and one in the UK in 1996 (Million Women Study).[9] Several meta-analyses have also been performed,[10–14] but most of them have been unable to demonstrate any association between regular mobile phone use (yes/no) and brain tumours, A recent meta-analysis performed by Repacholi *et al*[15] reported no association (OR=1.1; 95% CI 0.9 to 1.3 for gliomas, OR=0.9; 95% CI 0.8 to 1.1 for meningiomas), whatever the delay since first use. However, beyond these overall risks, some results deserve specific attention. The Interphone study showed an increase in the risk of glioma in the group with the longest duration of use (≥1640 h) (OR=1.4; 95% CI 1.0 to 1.9), higher for ipsilateral use and temporal tumours. This association was not

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observed for meningiomas (OR=1.15; 95% CI 0.81 to 1.62).[16] Similar results were obtained in some meta-analyses, which showed an increased risk for gliomas and acoustic neuromas with long-term (over 10 years),[14] or long duration use (≥1640 h),[12] ipsilateral use,[14] and temporal location of the tumour.[12] By contrast, the two cohorts that did not face recall bias, showed no increased risk of glioma or meningioma.[8 9]

As mobile phone use is a recent phenomenon, the uncertainties are larger for slow-growing tumours, such as meningiomas and for long-term use, so exposure assessment is a major challenge and may contribute to the heterogeneity between studies. On the basis of these data, the International Agency for Research on Cancer (IARC) classified RF-EMF as possibly carcinogenic to humans (group 2B) in 2011.[17] Since the aetiology of brain tumours is still largely unknown, additional studies are needed.

The objective of our study was to investigate the relationship between brain tumours and mobile phone use among adults in France.

METHODS

CERENAT is a multicenter population-based case-control study initiated in 2004 and designed to study the role of environmental and occupational factors in the occurrence of primary central nervous system (CNS) tumours in adults.

Population

CERENAT cases were all subjects aged 16 years and over, with a benign or malignant CNS tumour diagnosed between June 2004 and May 2006, and living in one of four French areas (Gironde, Calvados, Manche, Hérault) at diagnosis. Cases were identified with the collaboration of a network of practitioners involved in the diagnosis and therapeutic management of patients and, with the aim of being exhaustive, from population-based cancer registries. All diagnoses were established by either a neuropathological or, for cases with no histological diagnosis, a clinical and radiological assessment. Primary brain tumours with the following ICDO-3 topography codes were included: C70.0-C70.9, C71.0-C71.9 and C72.2-C72.9. Patients with recurrent tumours, metastases, pituitary tumours, genetic syndrome or AIDS were excluded. Cases were grouped according to morphology codes as gliomas, meningiomas, acoustic neuromas, lymphomas and other unspecified primary brain tumours.[18] In this analysis, only cases of gliomas and meningiomas were considered. Medullary tumours were excluded because the exposure of the spinal cord to RF-EMF from mobile phone use is significantly lower.

For each case, two controls with no history of CNS tumour were randomly selected from the local electoral rolls during the period 2005–2008, individually matched on age (±2 years), sex and department of residence.

Data collection

Data were collected through standardised questionnaires delivered as face-to-face non-blinded structured interviews by trained interviewers. When cases were in a severe clinical condition or deceased, a proxy was invited to complete a simplified questionnaire, which was subsequently completed by their matched controls. The questionnaire covered sociodemographic characteristics, medical history, lifestyle and detailed occupational and environmental data.

Assessment of mobile phone use

A detailed questionnaire including a set of questions on phone use was completed by all subjects regarding themselves as regular users (ie, phoning at least once a week for 6 months or more) (see online supplementary appendix 1). For each new mobile phone or major change of use, the same questionnaire was completed again. Information concerning each mobile phone included: phone model (analogue or digital); beginning and end dates for the use of the phone; average number and duration of calls made and received per month during each use period; shared or individual use; occupational or personal use and hands-free kit use. Duration of calls per month was reported by the subjects or assessed from duration of cards or packages that subjects reported to use monthly (4.5% of the mobile phone users; 5.2% and 3.1% for cases and controls, respectively). Only the dates of use and duration of calls were sought from proxies and their matched controls in the simplified questionnaire.

Potential confounders

The following potential confounders were considered: level of education (primary school or less, secondary school, high school and university), smoking (non-smokers, former smokers, current smokers), alcohol consumption (classified as excessive in men over three glasses of wine, cider, beer or spirits per day, and over two glasses per day in women).

Potential occupational confounders were identified from detailed job calendars, and from specific questions about exposure to pesticides, extremely low-frequency electromagnetic fields (ELF-EMF), RF-EMF, and ionising radiation.[19 20] Specifically, pesticide exposure was defined as having performed treatment tasks on crops, gardens, wood, or other circumstances in any job during life. Subjects were classified as occupationally exposed to ELF-EMF if they had worked with welding equipment, grinding machines, induction or microwave ovens, electric machines in the medical sector, industrial machinery in the wood, textile, building, food processing and steel sectors; in the electronics industry; or near power lines. Concerning RF-EMF, jobs with exposure to metal detectors, demagnetisers, porticos or transmission devices were taken into account. Subjects reporting exposure to radioactive sources, use of equipment emitting or measuring radiation, or working at a nuclear site, were considered occupationally exposed to ionising radiation.

Analysis

The date of diagnosis was taken as the index date for each case and its two matched controls. Phone use during the year before the index date was not taken into account in the exposure assessment for accounting for a potential induction period and to eliminate any reverse causality bias due to prodromal effects. The reference category for all exposure variables comprised persons who were not regular phone users. Mobile phone exposure was assessed using the number of years since first regular use, average length of calls per month (hours), average number of calls per day, cumulative lifetime duration of calls (hours) and cumulative lifetime number of calls. Cumulative lifetime duration and number of calls were the sum of duration of calls and number of calls for each mobile phone reported. For all subjects using a hands-free kit or sharing their phone less than 50% of time, 50% of time, more than 50% of time and all the time, cumulative duration and number of calls (for hand-free kit only) were weighted by coefficients of 0.75, 0.50, 0.25 and 0.10, respectively.

Different aspects of mobile phone use were grouped into a number of categories for the analysis: time since first use was in three categories ((1–4), (5–9) and ≥10 years); average time of calls in four categories (<2, (2–4), (5–14) and ≥15 h/month);

average number of calls in four categories (≤1, (2–4), (5–9) and ≥10 calls per day); and duration and number of calls into five categories based on the distribution of values observed in controls (<25th, (25–49th), (50–74th), (75–89th), ≥90th percentile). The latter category was retained because of the large range of values and in accordance with previous findings.[16]

Conditional logistic regression for matched sets was used to estimate ORs and 95%CIs. All statistical tests were two-sided, and a global test for each categorical indicator was performed. Confounders were selected using the purposeful selection algorithm,[21] which combines the principles of significance and change-in-estimate in selecting variables for a final model. Each indicator was analysed separately and adjusted for confounders. Two sensitivity analyses were performed: the first one excluded proxy-interviews, as information was supposed more uncertain than the one collected from individuals themselves, and the second one excluded non-regular users and used the lowest category of exposure as the reference. Indeed, non-regular phone users were more often men, younger, more educated and more frequently occupationally exposed to RF-EMF, so that they could also differ in other unmeasured factors. Exposure lagging of 2 and 5 years before the index date was also analysed.

Stratified analyses were performed, and adjusted ORs were re-estimated in strata of tumour location, type of use (occupational/personal only), place of use (urban only/urban and rural), side of use (ipsilateral/contralateral) and phone model. The rationale for stratifying on occupational use was the consideration that it corresponded to a specific profile of use, with more frequent and shorter calls, often made in outdoor settings, potentially with different phone technology for devices being working tools. Side of use was considered as ipsilateral if the phone was used on the same side as the tumour or on both sides. It was defined as contralateral if the phone was used on the opposite side to the tumour. No laterality was assigned for median tumour. Analyses were performed for cases with ipsilateral use or no use and their matched controls, and then for cases with contralateral use or no use and their matched controls. Owing to the restricted number of matched case-control sets within each stratum, unconditional logistic regression adjusting for age and sex and for confounders was used for the stratified analyses on different mobile phone uses (type, place, phone model). For each analysis, mobile phone users in a stratum were compared with all non-regular users. We present the adjusted ORs for the last decile of cumulative duration (heavy mobile phone users).

Analyses were performed with the software SAS, V.9.2 (SAS Institute, Cary, North Carolina, Etats-Unis, USA).

RESULTS

Population characteristics

Out of the subjects defined as eligible, 95% of cases and 61% of controls were contacted, and a total of 596 (73%) cases and 1192 (45%) controls were finally included in the CERENAT study. Participation rate was 66% for glioma and 75% for meningioma cases. The main reasons for non-participation were refusals, severe condition or death without proxy. Non-included cases were older than included cases (mean age: 63 vs 58 years for gliomas and meningiomas). After exclusion of acoustic neuromas (n=42), lymphomas and unspecified brain tumours (n=56), medullar tumours (n=50), and persons with missing data on regular mobile phone use (two controls for gliomas plus one meningioma case and his two controls), 1339 subjects were analysed: 253 cases and 504 controls for gliomas; 194 cases and 388 controls for meningiomas. For gliomas and meningiomas,

Table 1 Description of study population. CERENAT, 2004–2006, France

	Gliomas (N=757)			Meningiomas (N=582)		
	N*	Cases (n=253) n (%)	Controls (n=504) n (%)	N*	Cases (n=194) n (%)	Controls (n=388) n (%)
Age (mean±SD)	757	56.4±15.4	56.4±15.3	582	60.4±11.0	60.2±11.0
Sex	757					
Men		144 (56.9)	287 (56.9)	582	48 (24.7)	96 (24.7)
Women		109 (43.1)	217 (43.1)		146 (75.3)	292 (75.3)
Simplified questionnaire	757	63 (24.9)	126 (25.0)	582	12 (6.2)	24 (6.2)
Level of education	754			582		
Primary school or less		60 (23.8)	84 (16.7)		55 (28.4)	103 (26.5)
Secondary school		91 (36.1)	160 (31.9)		77 (39.7)	114 (29.4)
High school		44 (17.5)	104 (20.7)		31 (16.0)	74 (19.1)
University		57 (22.6)	154 (30.7)		31 (16.0)	97 (25.0)
Tobacco	751			582		
Non-smoker		105 (41.8)	225 (45.0)		106 (54.6)	215 (55.4)
Former smoker		90 (35.9)	181 (36.2)		64 (33.0)	113 (29.1)
Current smoker		56 (22.3)	94 (18.8)		24 (12.4)	60 (15.5)
Alcohol†	567			546		
Moderate or no consumption		157 (82.6)	304 (80.6)		156 (85.7)	304 (83.5)
Excessive consumption		33 (17.4)	73 (19.4)		26 (14.3)	60 (16.5)
Occupational exposure						
Pesticides	757	36 (14.2)	46 (9.1)	582	15 (7.7)	32 (8.2)
Radiofrequencies	751	15 (6.0)	38 (7.6)	579	5 (2.6)	10 (2.6)
Ionising radiations	748	16 (6.4)	52 (10.4)	581	4 (2.1)	19 (4.9)
Extremely low frequencies	723	70 (28.9)	128 (26.6)	578	28 (14.5)	50 (13.0)

*Data available for analysis.
†Only for detailed questionnaire respondents.

neuropathological assessment represented 96% of diagnoses, and clinical and radiological assessment 4%.

Median time between the index date and interview was 6 months (IQR: 4, 10) for cases, and 21 months (IQR: 16, 30) for controls, similar for gliomas and meningiomas. The proportion of proxy interviews was 25% for gliomas and 6% for meningiomas (table 1). The average age was 56 years for gliomas and 60 years for meningiomas, and women represented 43% and 75% of the population, respectively. The level of education was higher in controls than in cases ($p<10^{-3}$).

Mobile phone use

Regular use was reported by half the total population, and in the same proportion in cases and controls, (55% for gliomas cases and controls, and 44% for meningiomas cases and controls). On average, users reported having used two different phones in their lifetime. One-third of regular users were occupational users, and 27% of users shared at least one of their phones with someone, but most of them (55%) were the main users. A hands-free kit was used by only 14% of the individuals. Among 64% of specified phone models, most (92%) were digital and a few (8%) were analogue. Table 2 presents characteristics of mobile phone use. Only 12% of the individuals used their phone for 10 years or more (45% for 1–4 years, and 43% for 5–9 years). The median cumulative lifetime duration of calls was 115 h (IQR: 41, 383) with values ranging from 0.7 to 18 612 and 0.2 to 7290 for glioma cases and controls, respectively, and from 3.8 to 4845 and 0.8 to 16 000 for meningioma cases and controls, respectively. The median calling time was 2.7 h/month (IQR: 1.2, 7.5) with values ranging from 0.1 to 198 and 0 to 91 h/month for glioma cases and controls, respectively, and from 0.2 to 100 and 0.1 to 200 for meningioma cases and controls.

Mobile phone users were more often men than non-users (49% vs 38%, $p<10^{-3}$). They were also younger (median 54 vs 66 years old, $p<10^{-3}$), more educated (university level for 35% vs 16%, $p<10^{-3}$), and more occupationally exposed to RF-EMF (7% vs 4%, p=0.02).

Gliomas

Univariate analysis

The proportion of regular users was comparable in cases (57%) and controls (54%), and mobile phone use characteristics are presented in table 2. An association with gliomas was observed in subjects with the longest cumulative lifetime duration of calls (≥90th percentile ie, 896 h) (OR=2.33; 95% CI 1.17 to 4.67). These results were unchanged when weighting the values for shared use and hands-free kit use, and when excluding simplified questionnaire respondents.

Multivariate analyses

A slight positive association was observed for gliomas in users versus non-users (OR=1.24; 95% CI 0.86 to 1.77) (table 3). Risks tended to increase with time since first use. An association was found with average time of calls per month (*global* $p<10^{-3}$) and with average number of calls per day (*global* p=0.04). The increase in risk as compared to non-regular users, was observed for an average of more than 15 h of calls per month (OR=4.21; 95% CI 2.00 to 8.87). Risks increased with cumulative duration of calls (*global* p=0.02), but not with cumulative number of calls (*global* p=0.41). The increase in risk was statistically significant only in the 90th percentile for cumulative duration of calls (OR=2.89; 95% CI 1.41 to 5.93) and cumulative number of calls (OR=2.10; 95% CI 1.03 to 4.31).

Analyses excluding proxies provided similar results (table 4) and the ORs were almost unchanged when weighting for shared use and hands-free kit use. In sensitivity analyses excluding non-regular users, and considering the first class of regular mobile phone users as reference, we observed a trend for an increased risk with the cumulative duration of calls that was statistically significant for the last decile (OR=0.88 (0.44 to 1.78); OR=1.30 (0.66 to 2.55); OR=1.96 (0.97 to 3.96); OR=2.53 (1.17 to 5.46)).

Meningiomas

Univariate analysis

The proportion of regular users was comparable in cases (41%) and controls (45%). A positive association was observed in subjects with the longest cumulative duration of calls (≥896 h) (OR=2.29; 95% CI 0.94 to 5.58), a result also observed in subjects with the highest number of calls (≥18 360 calls) (OR=1.73; 95% CI 0.66 to 4.50).

Multivariate analyses

No association was observed for meningiomas when considering regular phone users versus non-users (OR=0.90; 95% CI 0.61 to 1.34). An increased OR for more than 15 h of calls per month was observed for meningiomas (OR=2.01; 95% CI 0.84 to 5.22). For cumulative duration of calls, a statistically significant association was observed in the last decile OR=2.57 (95% CI 1.02 to 6.44).

The average number of calls per day was not associated with meningiomas, and the risk was not significantly increased with the cumulative number of calls.

Table 2 Mobile phone use among regular users (n=417/757 gliomas strata; n=253/582 meningiomas strata). CERENAT, 2004–2006, France

	Gliomas				Meningiomas			
	Cases (n=143)		Controls (n=274)		Cases (n=80)		Controls (n=173)	
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)
Time since first use (years)	138	6.0 (4.0, 8.9)	270	5.3 (3.5, 7.4)	79	5.3 (3.3, 7.3)	169	4.9 (3.3, 7.2)
Calling time per month (hours)	124	5.0 (1.5, 13.0)	237	2.5 (1.1, 6.0)	71	2.0 (1.0, 9.0)	154	2.4 (1.3, 5.0)
Number of calls per day*	111	2.9 (0.7, 7.0)	197	1.5 (0.7, 5.0)	69	0.9 (0.4, 4.0)	146	1.5 (0.5, 4.0)
Cumulative lifetime duration of calls (hours)	124	210 (63, 602)	237	106 (34, 338)	71	66 (25, 504)	154	96 (35, 237)
Weighted cumulative lifetime duration of calls (hours)*	110	176 (55, 490)	198	79 (26, 318)	67	66 (15, 320)	145	69 (25, 154)
Cumulative lifetime number of calls*	111	2880 (816, 8316)	197	1980 (684, 7020)	69	1044 (344, 4800)	146	1572 (548, 5220)
Weighted cumulative lifetime number of calls*	111	2846 (640, 7280)	197	1575 (448, 6030)	69	1104 (216, 5280)	146	1165 (432, 4080)

*Only for detailed questionnaire respondents.

Table 3 Adjusted conditional logistic regression for each mobile phone use indicator. CERENAT, 2004–2006, France

		Gliomas					Meningiomas			
	N*	Ca (n=253)	Co (n=504)	OR† (95% CI)	p Value‡	N*	Ca (n=194)	Co (n=388)	OR§ (95% CI)	p Value‡
Regular mobile phone user	745				0.25	582				0.61
No		107	226	Reference			114	215	Reference	
Yes		142	270	1.24 (0.86 to 1.77)			80	173	0.90 (0.61 to 1.34)	
Time since first use (years)	727				0.17	577				0.52
Not regular user		107	219	Reference			114	215	Reference	
(1–4)		49	122	0.88 (0.56 to 1.39)			36	85	0.79 (0.49 to 1.27)	
(5–9)		66	111	1.34 (0.87 to 2.06)			33	71	0.97 (0.58 to 1.61)	
≥10		22	31	1.61 (0.85 to 3.09)			10	13	1.57 (0.64 to 3.86)	
Average calling time per month (hours)	677				$<10^{-3}$	546				0.04
Not regular user		107	211	Reference			114	207	Reference	
<2		40	98	0.91 (0.57 to 1.46)			35	63	1.16 (0.68 to 1.97)	
(2–4)		19	62	0.57 (0.30 to 1.10)			13	52	0.43 (0.21 to 0.86)	
(5–14)		36	53	1.70 (0.97 to 2.99)			12	27	0.75 (0.35 to 1.61)	
≥15		29	22	4.21 (2.00 to 8.87)			11	12	2.01 (0.84 to 5.22)	
Average number of calls per day¶	520				0.04	515				0.49
Not regular user		67	145	Reference			106	194	Reference	
<2		33	77	0.91 (0.54 to 1.54)			35	59	1.12 (0.67 to 1.87)	
(2–4)		35	69	1.18 (0.69 to 2.03)			19	57	0.60 (0.32 to 1.10)	
(5–9)		23	22	2.74 (1.33 to 5.65)			9	19	0.87 (0.37 to 2.08)	
≥10		20	29	1.78 (0.88 to 3.59)			6	11	0.83 (0.26 to 2.60)	
Cumulative duration of calls (hours)	677				0.02	546				0.06
Not regular user		107	211	Reference			114	207	Reference	
<43		24	63	0.83 (0.48 to 1.44)			25	44	1.12 (0.61 to 2.04)	
(43–112)		20	55	0.77 (0.42 to 1.41)			17	40	0.85 (0.45 to 1.61)	
(113–338)		28	58	1.07 (0.60 to 1.90)			11	40	0.52 (0.25 to 1.07)	
(339–895)		28	37	1.78 (0.98 to 3.24)			5	21	0.52 (0.18 to 1.45)	
≥896		24	22	2.89 (1.41 to 5.93)			13	9	2.57 (1.02 to 6.44)	
Cumulative number of calls¶	520				0.41	515				0.13
Not regular user		67	145	Reference			106	194	Reference	
<660		23	47	1.06 (0.59 to 1.91)			30	42	1.36 (0.77 to 2.40)	
(660–2219)		27	58	1.06 (0.59 to 1.91)			12	38	0.59 (0.29 to 1.21)	
(2220–7349)		28	45	1.48 (0.79 to 2.76)			11	35	0.59 (0.28 to 1.24)	
(7350–18 359)		12	23	1.30 (0.60 to 2.83)			6	21	0.52 (0.20 to 1.39)	
≥18 360		21	24	2.10 (1.03 to 4.31)			10	10	1.73 (0.64 to 4.63)	

*Data available for analysis.
†OR for each indicator adjusted for level of education and ionising radiation exposure.
‡p Values for global test.
§OR for each indicator adjusted for level of education.
¶Only for detailed questionnaire respondents.
Ca, Cases; Co, controls.

As previously, excluding proxies did not have any effect in the results (table 4). In sensitivity analyses excluding non-regular users, no trend for an increased risk with the cumulative duration of calls was observed when restricting to the regular mobile phone users.

Heavy users and stratified analyses

Among heaviest users (cumulative duration ≥896 h), time since first use was occasionally less than 5 years (11%) but mostly 5–9 years (49%) and 10 years and more (40%) (table 5). Thirty-three per cent of them were commercial agents or sales people, and 22% were chief operating officers or production and operation managers. Sixty-two per cent of them reported occupational mobile phone use. Their median cumulative duration of calls was 1925 h, corresponding to 54 min/day (IQR: 30, 96 min), with a maximum of 6.6 h/day.

For gliomas, considering a 5-year latency period led to an increased OR for the last decile compared with non-regular users (5.30; 95% CI 2.12 to 13.23). Temporal location of the tumour presented a higher OR compared with the frontal one. The risk of glioma with occupational use was tripled (OR=3.27; 95% CI 1.45 to 7.35) and exclusively urban setting use was associated with an OR=8.20 (1.37, 49.07). A positive association was observed for ipsilateral tumours while it was negative for contralateral tumours (see online supplementary appendix 2).

For meningiomas, CIs were wider because of the smaller sample size. However, extending the latency period to 2 or 5 years before the index date appeared to decrease the risk. The higher OR was observed for temporal meningiomas, and the risk for ipsilateral tumour was slightly higher than for contralateral tumours.

Finally, same trends were observed in men and women and with regards to age, with higher associations for men and for 30–59-year-old subjects (data not shown).

DISCUSSION

This study provides additional data on the relationship between RF-EMF exposure and brain tumours. No statistically significant

Table 4 Adjusted conditional logistic regression after exclusion of simplified questionnaires. CERENAT, 2004–2006, France

	Gliomas					Meningiomas				
	N*	Ca (n=190)	Co (n=378)	OR† (95% CI)	p Value‡	N*	Ca (n=182)	Co (n=364)	OR§ (95% CI)	p Value‡
Regular mobile phone user	568				0.16	546				0.56
No		67	153	Reference			106	200	Reference	
Yes		123	225	1.33 (0.89 to 1.98)			76	164	0.89 (0.60 to 1.32)	
Time since first use (years)	554				0.36	541				0.63
Not regular user		67	148	Reference			106	200	Reference	
(1–4)		47	105	1.04 (0.64 to 1.69)			35	82	0.78 (0.48 to 1.28)	
(5–9)		58	93	1.45 (0.91 to 2.33)			31	65	0.96 (0.57 to 1.62)	
≥10		14	22	1.45 (0.68 to 3.08)			9	13	1.42 (0.56 to 3.55)	
Average calling time per month (hours)	518				$<10^{-3}$	510				0.08
Not regular user		67	143	Reference			106	192	Reference	
<2		36	78	1.01 (0.61 to 1.69)			31	60	1.05 (0.60 to 1.81)	
(2–4)		16	53	0.59 (0.29 to 1.21)			13	47	0.45 (0.22 to 0.91)	
(5–14)		33	47	1.78 (0.99 to 3.22)			12	26	0.78 (0.36 to 1.68)	
≥15		25	20	4.04 (1.84 to 8.86)			11	12	2.02 (0.81 to 5.04)	
Cumulative duration of calls (hours)	518				0.07	510				0.07
Not regular user		67	143	Reference			106	192	Reference	
<43		22	50	0.93 (0.52 to 1.68)			24	42	1.10 (0.60 to 2.04)	
(43–112)		18	50	0.81 (0.43 to 1.54)			14	39	0.71 (0.36 to 1.40)	
(113–338)		27	46	1.43 (0.76 to 2.67)			11	36	0.55 (0.26 to 1.16)	
(339–895)		24	32	1.76 (0.93 to 3.32)			5	19	0.56 (0.20 to 1.60)	
≥896		19	20	2.54 (1.19 to 5.41)			13	9	2.47 (0.99 to 6.19)	
Weighted cumulative duration of calls (hours)	518				0.03	510				0.19
Not regular user		67	143	Reference			106	192	Reference	
<29		19	55	0.73 (0.39 to 1.35)			24	40	1.22 (0.64 to 2.31)	
(29–86)		20	48	0.97 (0.52 to 1.78)			14	44	0.56 (0.28 to 1.11)	
(87–326)		31	47	1.56 (0.86 to 2.83)			13	33	0.72 (0.36 to 1.46)	
(327–835)		22	32	1.62 (0.84 to 3.14)			5	17	0.57 (0.19 to 1.67)	
≥836		18	16	2.83 (1.30 to 6.17)			11	11	1.74 (0.69 to 4.41)	
Weighted cumulative number of calls	520				0.14	515				0.59
Not regular user		67	145	Reference			106	194	Reference	
<476		19	51	0.80 (0.43 to 1.47)			24	38	1.18 (0.65 to 2.15)	
(476–1649)		26	49	1.26 (0.70 to 2.28)			17	45	0.70 (0.37 to 1.31)	
(1650–6269)		35	50	1.71 (0.95 to 3.09)			13	34	0.74 (0.36 to 1.51)	
(6270–14 699)		11	25	1.14 (0.52 to 2.53)			7	19	0.63 (0.23 to 1.68)	
≥14 700		20	22	2.11 (1.03 to 4.33)			8	10	1.30 (0.43 to 3.89)	

Non-weighted average number of calls per day, and cumulative number of calls, are previously presented only for detailed questionnaire respondents in table 3.
*Data available for analysis.
†OR for each indicator adjusted for level of education and ionising radiation exposure.
‡p Values for global test.
§OR for each indicator adjusted for level of education.
Ca, Cases; Co, controls.

increase in brain tumours was observed in regular users versus non-users. In the heaviest users, however, we found a positive association that was stronger for gliomas and that increased with a 5-year latency before diagnosis. This association was more pronounced for occupational users and in urban settings.

This multicentric study was conducted on the general population, and covered various socioeconomic statuses and environmental and occupational exposures. Cases were included from a clinical network supported by population-based cancer registries, thereby ensuring the reliability of the diagnoses. Controls were randomly selected from the electoral rolls, which include 90% of persons over 18 years, and are representative of the French adult population regarding age and sex.[22] The participation rates (66% and 75% for glioma and meningioma cases, respectively, and 45% for controls) were lower than those reported in previous studies,[23–26] but similar to those of the Interphone study.[16] Unfortunately, the lack of a questionnaire for non-participants prevented us from accurately assessing selection bias. However, the study was presented to participants as dealing with environmental and occupational factors and health in general, and was not focused on mobile phone use. Half the study population reported a regular use, and 63% of 30–59-year-old persons (66% in cases and 62% in controls). This prevalence is slightly higher than in the French part of the Interphone study (54% of regular use for 30–59-year-old cases and 56% for controls in 2000–2004[27]), but comparable with mobile phone use reported in France in 2003, (62% in 40–59-year-old persons).[28] Thus, non-participation had no evident reason to be specially related to mobile phone use.

RF-EMF exposure from mobile phones was assessed with a face-to-face standardised questionnaire, thus limiting a priori misinterpretation of questions by individuals, and missing responses. It was not possible to blind the case/control status of subjects, but the interviewing team endeavoured to standardise

Table 5 Associations between heavy mobile phone use (last decile of cumulative duration) and tumours according to censorship, tumour location and characteristics of use. CERENAT, 2004–2006, France

	Gliomas					Meningiomas				
	Cases N (% Not user/% last decile)*		Controls N (% Not user/% last decile)*		OR† (95% CI)	Cases N (% Not user/% last decile)*		Controls N (% Not user/% last decile)*		OR‡ (95% CI)
1-year censorship	**231**	**(46.3/10.4)**	**446**	**(47.3/4.9)**	**2.89 (1.41 to 5.93)**	**185**	**(61.6/7.0)**	**361**	**(57.3/2.5)**	**2.57 (1.02 to 6.44)**
2-year censorship	231	(48.9/10.4)	446	(50.4/4.7)	3.03 (1.47 to 6.26)	185	(65.4/6.5)	361	(61.5/2.5)	2.40 (0.96 to 6.05)
5-year censorship	231	(67.1/7.8)	446	(71.5/2.2)	5.30 (2.12 to 13.23)	185	(80.5/2.7)	361	(79.8/1.9)	1.44 (0.43 to 4.80)
Temporal	68	(51.5/10.3)	133	(46.6/3.8)	3.94 (0.81 to 19.08)	28	(57.1/7.1)	54	(64.8/1.9)	7.89 (0.48 to 130.14)
Frontal	76	(46.1/10.5)	148	(49.3/6.1)	1.87 (0.62 to 5.64)	65	(67.7/7.7)	125	(56.0/1.6)	4.82 (0.78 to 29.63)
Other locations	87	(42.5/10.3)	165	(46.1/4.8)	3.61 (1.00 to 12.96)	92	(58.7/6.5)	182	(56.0/3.3)	1.60 (0.47 to 5.46)
Occupational use§	152	(70.4/11.2)	304	(75.7/5.3)	3.27 (1.45 to 7.35)					–¶
Personal use only§	170	(62.9/1.2)	364	(63.2/2.2)	0.61 (0.12 to 3.26)					–¶
Urban use only§	123	(87.0/3.3)	259	(88.8/0.8)	8.20 (1.37 to 49.07)	125	(91.2/1.6)	230	(93.5/0.9)	2.72 (0.36 to 20.78)
Urban and rural use§	185	(57.8/7.6)	404	(56.9/5.4)	2.03 (0.93 to 4.40)	162	(70.4/6.8)	340	(63.2/2.6)	2.12 (0.81 to 5.57)
Ipsilateral	167	(64.1/5.4)	325	(53.2/2.2)	2.11 (0.73 to 6.08)	140	(81.4/4.3)	276	(59.1/1.4)	2.29 (0.58 to 8.97)
Contralateral	144	(74.3/6.3)	278	(53.2/4.3)	0.66 (0.23 to 1.89)	144	(79.2/4.2)	280	(60.4/2.1)	1.18 (0.34 to 4.12)
Analogue§	115	(93.0/4.3)	253	(90.9/2.0)	3.75 (0.97 to 14.43)					–¶
Digital only§	167	(64.1/6.0)	337	(68.2/3.3)	2.71 (1.03 to 7.10)					–¶

*Last decile of cumulative duration of calls : ≥896 h.
†OR adjusted for level of education and ionising radiation exposure
‡OR adjusted for level of education .
§Unconditional logistic regression adjusted for age, sex and level of education ± ionising radiation exposure. For each stratum, mobile phone users in the last class of cumulative duration corresponding to a specific use were compared with all non-users (for gliomas n=107 Ca/230 Co and for meningiomas n=114 Ca/215Co).
¶No estimations due to low numbers of individuals.
Result in bold corresponds to the results of the main analysis in Table 3 which can be compared to those of the following lines.

data collection in cases and controls at all stages. The delay between index date and interview was longer for controls, but we censured information on phone use after the index date, and no increase in mobile phone use was observed in the period elapsed since index date in controls.

Some interviews had to be conducted with a proxy because of the health status of the cases. A simplified questionnaire was then used in cases and in matched controls to prevent any differential bias related to simplified questions, even though the quality of data obtained from proxies remains questionable for cases. Nevertheless, analyses excluding simplified questionnaires showed comparable results.

As in any retrospective analysis and in other mobile phone studies performed at the same period, we found indication of recall bias regarding exposure data. Several studies have tried to measure recall bias by crossing the individuals' reports with operators' data, published after the beginning of our study. The Interphone validation studies concluded that individuals tended to slightly underestimate the number of calls and overestimate call duration, but no difference was observed between cases and controls.[27 29–31] A Finnish study on the validity of self-reported mobile phone use confirmed this trend.[32] An exception would exist for a long time before the interview in the Interphone validation study, where an overestimation was observed, more pronounced for cases than for controls.[30] By contrast, two studies found an overestimation of the number and duration of calls, that increased with phone use.[33 34] Thus, like in the Interphone study, finding significant results only in the last decile could suggest that some subjects among the heavy users over-reported their use. We individually checked all extreme values (the maximum was 200 h/month, ie, 6.7 h/day) by reviewing together mobile phone use history and occupational calendars. The information was considered consistent when a plausible reason for the duration was given, for instance, working outdoors, or travelling and having the necessity to contact customers or collaborators to manage appointments or prospect affairs. If recall bias is more pronounced in heaviest users, it is likely that exposure values in the last decile are overestimated. Nevertheless, this should not impact the association we observed when considering exposure in categories.[27] Moreover, if this error is non-differential,[30] associations should be underestimated, and although a differential bias cannot be excluded, underestimation seems to be more likely to occur.[35] To improve exposure assessment, we also considered phone sharing, use of a hands-free kit, occupational use, and urban and rural settings. Since some of the additional analyses were limited by the low numbers, even if most of the estimates show acceptable precision, caution should be taken when interpreting the results.

The lack of statistically significant association when comparing users to non-users is consistent with several previous reports.[16 25 26 33 36 37] Consistent with previous studies, we found an increased risk in the heaviest users, especially for gliomas.[16 24] The statistically significant increase we found was for cumulative duration above about 900 h of use, while the threshold was 1640 h in the Interphone study,[16 37] and ranged between 65 and 2000 h in the various swedish studies.[16 23 24 37] Such variations in phone use patterns across different studies and populations impede the definition of a reliable threshold and even to be sure of its reality. Actually, a dose-effect relationship would be more consistent with the role of RF-EMF in the development of tumours. In line with this idea, the trend between categories of use we found in sensitivity analyses for gliomas when considering the lowest phone use (and not non-users) as reference, appears more suggestive of a possible role of RF-EMF.

In our study, we found an increased risk in those subjects reporting a prolonged use, making numerous calls, whose use was especially occupational and more often in urban areas (without correlation between these specific uses). To date, it has not been possible to determine whether the increased risk is related to use over many years or to the cumulative duration of

calls. In our study, time since first use was not associated with the presence of a tumour, which may be partly due to the low number of users for 10 years and more. This issue remains controversial, as some studies found an increased risk with high use over a short period,[16] while others demonstrated a risk for prolonged use.[23 24 33 37] Moreover, by censoring exposure 2 years and 5 years before diagnosis, we observed higher associations for gliomas. This could be due to an induction effect of exposure on the emergence of the tumour.

Assuming that RF-EMF emitted by mobile phones are a risk factor for brain tumours owing to their proximity to the head, an increased association for temporal tumours and side of phone use was expected, in accordance with the results of some studies,[16 23 37 38] but not all of them.[33] In our study, the increase in risk was more prominent when considering tumour location, especially for meningiomas, than side of phone use, which could be due to uncertainties in subjects reporting side of use.

As expected, we found a higher risk for temporal location than for frontal one, which was more pronounced for meningiomas. Our results for gliomas are difficult to interpret since the risk for 'other locations' is the same as for temporal location. Ipsilateral associations were higher than contralateral ones, but we observed this result whatever the level of phone use and the indicator (see results in online supplementary appendix 2). If we consider that reporting bias mainly concerns heavy users, we would expect increased ORs for ipsilateral use mostly in the higher exposure category. In this circumstance, an overall increase may reflect an overall over-reporting of ipsilateral use by cases, or a real effect of ipsilateral use regardless of the level of use.

Finally, we observed increased OR for urban use for gliomas, a result inconsistent with the hypothesis of a higher RF power output during calls in rural areas, documented by some Swedish study.[39–41] However, our results are consistent with a recent international study showing no difference between rural and urban exposition in most countries except in Sweden,[42] and a Hardell study when considering gliomas separately.[43] Several parameters associated with rural/urban setting are susceptible to impact exposure, such as the concomitant residential exposure and the differences in the types of use and characteristics of users. Additional data including the influence of high density of base station allowing to use low output power for calls in urban areas, but leading to a high number of handovers, during which output power is highest, should be investigated further.

An increase in the incidence of primary brain tumours has been observed in the past decades in several countries. It has been explored whether these trends could be related to change in suspected risk factors, including mobile phone use.[44–48] Results obtained to date are not in favour of a correlation. However, temporal trends and differences between countries are not easy to interpret because of methodological limitation in the recording of brain tumours, including changes with time in recording procedure, and the lack of completeness concerning non-malignant tumours.

CONCLUSIONS

This case-control study provides additional data on the relationship between mobile phone use and brain tumours. Considering lifetime cumulative duration of calls, an increased risk appears among the heaviest users, often with occupational use and especially for gliomas. While this is consistent with some other studies, it is difficult to define a level of risk, if any, especially as mobile phone technology is constantly evolving. The rapid evolution of technology has led to a considerable increase in the use of mobile phones and a parallel decrease of RF-EMF emitted by the phones. Studies taking account of these recent developments, and allowing the observation of potential long-term effects will be needed.

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Mobile phone use and brain tumours in the CERENAT case-control study

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