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ARTICLE

Mobile Phone Use and Brain Tumors in Children and Adolescents: A Multicenter Case–Control Study

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Background It has been hypothesized that children and adolescents might be more vulnerable to possible health effects from mobile phone exposure than adults. We investigated whether mobile phone use is associated with brain tumor risk among children and adolescents.

Methods CEFALO is a multicenter case–control study conducted in Denmark, Sweden, Norway, and Switzerland that includes all children and adolescents aged 7–19 years who were diagnosed with a brain tumor between 2004 and 2008. We conducted interviews, in person, with 352 case patients (participation rate: 83%) and 646 control subjects (participation rate: 71%) and their parents. Control subjects were randomly selected from population registries and matched by age, sex, and geographical region. We asked about mobile phone use and included mobile phone operator records when available. Odds ratios (ORs) for brain tumor risk and 95% confidence intervals (CIs) were calculated using conditional logistic regression models.

Results Regular users of mobile phones were not statistically significantly more likely to have been diagnosed with brain tumors compared with nonusers (OR = 1.36; 95% CI = 0.92 to 2.02). Children who started to use mobile phones at least 5 years ago were not at increased risk compared with those who had never regularly used mobile phones (OR = 1.26, 95% CI = 0.70 to 2.28). In a subset of study participants for whom operator recorded data were available, brain tumor risk was related to the time elapsed since the mobile phone subscription was started but not to amount of use. No increased risk of brain tumors was observed for brain areas receiving the highest amount of exposure.

Conclusion The absence of an exposure–response relationship either in terms of the amount of mobile phone use or by localization of the brain tumor argues against a causal association.

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A steep rise in the popularity of mobile phones among children and adolescents in recent years has been reflected in both increased ownership and increased usage (1–3). One study (4) has indicated that most children start to use mobile phones when they are around 9–10 years old, but usage before school age is not uncommon. The increase in mobile phone use has raised concerns about possible adverse health effects. Brain tumors have been a main concern because when the handset is held to the head, the brain absorbs most of the radio frequency energy emitted by mobile phones. Moreover, it has been hypothesized (5) that children may be more vulnerable to radio frequency electromagnetic fields (RF EMFs) because they have a developing nervous system, their brain tissue is more conductive than that of adults (because of its higher water content and ion concentration), and RF EMFs penetrate into regions that are deeper in their brains [because the head circumference is smaller in children compared with adults (5)]. Recent modeling studies (6,7) have indicated that about twice as much mobile phone energy is absorbed in the peripheral brain tissues of children aged 5–8 years as in adults.

The radio frequency radiation emitted by mobile phone handsets has insufficient energy to directly damage DNA: It is nonionizing and its only known effect is heating. Hence, genotoxic effects such as DNA mutations or strand breaks cannot be directly linked to exposure to mobile phone radiation (8). The lack of genotoxicity of mobile phone radiation has been confirmed by experimental animal and laboratory studies (9,10). Overall, in vitro studies and experiments in mice [reviewed in (11)] have provided little evidence that mobile phone radiation is carcinogenic.

To date, no study has addressed the association between mobile phone use and the risk of brain tumors among children and adolescents. Studies in adults have shown no increase in risk among regular users but have been inconclusive regarding longer-term

heavy use of mobile phones (12). The recently published INTERPHONE study (13) found an increased risk for glioma among heavy users (cumulative call duration ≥ 1640 hours), but it is uncertain whether this reflects a true risk associated with the use of mobile phones or a spurious relationship due to recall bias or other methodological limitations (13,14). A study by Hardell et al. (15) reported that astrocytoma was much more common among adults who first used mobile phones before age 20 (odds ratio [OR] = 5.2) or who first used cordless phones before age 20 (OR = 4.4).

In 2006, we set up CEFALO, an international case–control study of the relationship between mobile phone use and risk of developing brain tumors in children and adolescents. Participants were children aged 7–19 years in Denmark, Sweden, Norway, and Switzerland. We collected data by means of face-to-face interviews with the subjects and their parents.

CONTEXT AND CAVEATS

Prior knowledge

No previous studies have examined whether mobile phone use among children and adolescents is associated with a difference in brain tumor risk.

Study design

The study included all 352 patients aged 7–19 who were diagnosed with brain tumors in 2004–2008 in Denmark, Sweden, Norway, or Switzerland and 646 age-, sex-, and region-matched controls. Mobile phone use was determined from interviews and, when available, from operator records. Odds ratios were determined for brain tumor incidence.

Contribution

Mobile phone users had no statistically significant difference in brain tumor risk compared with nonusers. Risk did not increase with the duration of mobile phone use. Nor was risk higher in the areas of the brain that came into closest proximity to a hand-held mobile phone.

Implications

The authors found little or no evidence that mobile phones increase brain tumor risk, and the single positive association could be explained by bias or chance.

Limitations

Most mobile phone usage data were based on the recall of children or adolescents and their parents. Brain tumors are rare, and the study was not statistically powered to detect small risk increases. Amount and duration of mobile phone use was relatively small and may have increased in this age-group since the time of this study.

From the Editors

Subjects and Methods

Study Population

CEFALO is an international case–control study performed in Denmark, Sweden, Norway, and Switzerland. The study period was approximately from January 1, 2004, through August 31, 2008, but varied slightly between study centers.

Case Eligibility and Ascertainment

All children and adolescents who were diagnosed during the study period with intracranial central nervous system tumors and who were aged 7–19 years at the time of diagnosis were eligible to become case patients. The brain tumors had to be coded as C71, D33.0–33.2, D33.9, D43.0–43.2, D43.9, or C72.9 according to the *International Classification of Diseases, tenth revision* (*ICD-10*) to be included. In addition, they had to fulfill the diagnostic criteria according to following morphology codes from the *International Classification of Diseases for Oncology, third edition* (*ICD-O-3*): ependymoma (9383, 9391–9393), astrocytoma (9384, 9400–9401, 9410–9411, 9420–9424, 9440–9442), primitive neuroectodermal tumor (PNET; 9470–9474, 9480, 9502–9504, 9508), other glioma (9380–9382, 9430, 9444, 9450–9451, 9460), other specified intracranial neoplasms (8743, 9064, 9071, 9080, 9161, 9390, 9412–9413, 9492–9493, 9505–9507, 9560), or unspecified intracranial neoplasms (8000–8005, 9990, 9999).

All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. We examined medical records for case patients to confirm the diagnosis and to establish the date of diagnosis, which was used as reference date in the exposure assessment. Date of diagnosis was defined as the date when the first diagnostic imaging was performed. Case patients were excluded if they were diagnosed with neurofibromatosis (Mb Recklinghausen; 12 patients) or tuberous sclerosis (one patient). Study participants who were completely deaf before the reference date and children with severe mental retardation were excluded (two patients and two control subjects). In addition, families with insufficient language skills to complete an interview, as judged by a nurse, treating physician, or project administrator, were excluded (15 patients and 36 control subjects).

Each country established procedures for identification of the case patients. In Denmark and Sweden, case identification was performed by a combination of reports from pediatric, oncology, and neurosurgery departments and from the population-based registries (the Danish National Cancer Registry, Childhood Cancer Registry, Pathology Registry, and National Patient Registry, and the Swedish Regional Cancer Registries, which also provide the data for the Swedish National Cancer Registry). In Norway, all case patients were identified from the population-based Norwegian National Cancer Registry and verified by the responsible physician. In Switzerland, case patients aged younger than 16 years at diagnosis were identified through the Swiss Childhood Cancer Registry, and case patients aged 16–19 years at diagnosis were identified through neurosurgery clinics, pathology departments, and cantonal general cancer registries.

Control Eligibility and Selection

We randomly selected two control subjects per case patient using population registries in the participating countries, matched by age (in Denmark, Sweden, and Switzerland, by year and month of birth; in Norway, by year of birth), sex, and geographical region. In Switzerland, a two-stage random sampling procedure was applied for the selection of control subjects in the absence of a national population registry. First, a community was randomly determined within the same language region as each patient, and second, the control subject was randomly selected from the

corresponding communal population registry. The reference date for control subjects was same as the date of diagnosis of the matched case patient.

Data Collection

Data collection started in June 2006 in all countries except Norway, where data collection started in December 2007. All case patients for whom physicians authorized contact and all control subjects were informed about the study and asked to participate (we did not receive authorization from the physicians of 19 case patients). The information letter explained the study focus on risk factors for brain tumors and did not mention mobile phones to minimize differential participation bias. The procedures varied between countries, depending on the requirements of local ethics review boards. If the case patient was deceased (36 cases), the parents were contacted at least 6 months after the death of the child, as requested by the treating physicians. The case patients and control subjects provided signed informed consent in all countries.

Whenever possible, the children were accompanied by at least one parent (preferably the mother) and were interviewed face to face by trained interviewers using a computer-assisted personal interview (CAPI) questionnaire (Denmark and Norway) or a paper version of the questionnaire (Switzerland and Sweden). In exceptional circumstances, telephone interviews were conducted with difficult-to-reach subjects (four control subjects) or an adapted paper version of the questionnaire was sent to the study participants (19 control subjects). Interviews with case patients and matched control subjects were mainly performed by the same interviewer. Interviewers from all centers received training at a joint workshop to ensure uniform data collection. The translations of the questionnaires were checked through back-translation to the master version (English), and the questionnaires were pilot tested in all participating countries. At all centers, control subjects who refused to participate in the study (n = 172) were asked to complete a short nonresponder questionnaire (85 were completed). A small number of nonparticipating case patients (n = 8) also completed the nonresponder questionnaire. Due to local ethical guidelines, it was not possible to send nonresponder questionnaires to case patients in Denmark when written refusals were received from case families. All case patients were interviewed within 5 years of diagnosis, and 63% were interviewed within 2 years of diagnosis.

Mobile Phone Exposure Assessment

All study participants were asked if they had ever spoken on a mobile phone more than 20 times during their lives and if the child ever owned a mobile phone before the reference date. Owners of a mobile phone were asked how many subscriptions they have had. For each subscription, the following information was asked: network operator, when the subscription was started and stopped, use of hands-free devices, preferred side of head during use, number of calls per day, and duration of calls (both in predefined categories of use). Major changes in usage within a subscription were also recorded.

For calculating exposure surrogates, we did not consider mobile phone use that occurred within 6 months before the reference date. All subjects who had an average of at least one call per week for at least 6 months based on their self-reported amount of phone use were classified as regular users of mobile phones (16). Additional calculated exposure variables for regular users were time since first use of mobile phones (years), cumulative duration of subscriptions (years), cumulative duration of use (hours), and cumulative number of calls. All cumulative exposure surrogates were corrected for the use of hands-free devices. For all time periods for which the subject reported the use of hands-free devices, the amount of phone use was reduced by 80%, 50%, or 20% depending on whether hands-free devices were used almost always, half of the time, or sometimes, respectively.

Study participants were asked to give consent to allow the researchers access to traffic data from mobile phone network operators. Data was provided by two network operators in Sweden, three in Denmark, and three in Switzerland. Operators were asked for data linked to a specific personal identification number, phone number or name, or a combination of any of the data given by the study participants. From the network operators, we received information about number of calls, duration of calls, as well as subscription start and end dates. In Switzerland, traffic data is deleted after 6 months. Thus, only data covering the period after the reference date were available in Switzerland. Only time since first subscription of phones could be used from the operator recorded data from Switzerland because this date is not routinely deleted.

Statistical Analysis

Odds ratios and 95% confidence intervals (CIs) were based on conditional logistic regression models for matched case–control studies (17). All statistical tests were two-sided. In the main analyses, the reference category for odds ratios consisted of subjects who were nonregular users or nonusers of mobile phones. Time since first use of mobile phones, cumulative duration of subscriptions, cumulative duration, and number of calls were categorized based on the distribution of these variables in control subjects who were regular users; the 50th and 75th percentiles were chosen as cutoffs to allow for the skewed data distribution. *P* values for tests of linear trend (in risk for brain tumors in relation to exposure) were calculated by means of a two-sided Wald test for regression models in which exposure was included as a continuous variable, and all subjects in a category were assigned the median value of their corresponding category (18).

We checked the impact of the following potential confounders on our analyses: highest attained educational level of either mother or father as a measure of socioeconomic status (SES; low: elementary school not completed; intermediate: elementary school, diploma school, or apprenticeship; high: university or technical college), family history of cancer (yes, no), past medical radiation exposure to the head (yes, no), maternal smoking during pregnancy (yes, no), past head injuries (yes, no), use of baby monitors (ie, wireless baby monitor or alarm used to remotely listen to sounds made by an infant) near the head (yes, no), use of cordless phones (cumulative duration and number of calls), contact with animals (yes, no), location where the child lived before age 6 (town or village with ≥200 inhabitants, farm, countryside), having siblings (yes, no), birth weight (continuous), born premature (yes, no), ever doctor-diagnosed asthma (yes, no), ever doctor-diagnosed atopic eczema (yes, no), and ever doctor-diagnosed hay fever (yes, no). We decided a priori to include confounders in our model if the odds ratio for the regular use of mobile

phones changed by 10% or more compared with the unadjusted model (19,20). Because none of the confounders that we considered changed the risk estimate for regular use of mobile phones by 10% or more, none of these confounders were included in the conditional logistic regression models presented.

To evaluate consistency of the results, we conducted analyses that were stratified by country, age-group (<15and ≥15 years), sex, tumor morphology (astrocytoma and other glioma compared with all other tumors), tumor location (highly exposed temporal, frontal lobes, and cerebellum compared with other parts of the brain), time between diagnosis and interview (≥1.5 and <1.5 years), time lag between interview of case patients and matched control subjects (>50 and ≤50 days), and latency periods of 2 and 5 years. Heterogeneity of the odds ratios between the strata was assessed with a likelihood ratio test that compared models that included only the main effects with those that included the interaction terms for the stratum-specific associations (21).

For the subset of subjects for whom operator data were available, analyses were made using the network operator recorded data to assess exposure. We used unconditional logistic regression models adjusted for geographical region, age and sex with operator recorded time since first subscription, cumulative duration of subscription, and, cumulative duration and number of calls as exposure variables. For the same subset of subjects, and for subjects for whom no operator recorded data were available, we also calculated unconditional logistic regression models using self-reported mobile phone use as exposure estimates, to compare the results for these two subsets of participants, and to allow an assessment of potential recall bias in self-reported mobile phone use.

In additional analyses, we compared the side of the head where users preferred to hold their mobile with the side of the head in which the tumor occurred by applying the method used in the INTERPHONE study (13). Each control subject was assigned the location of the tumor of the corresponding matched case patient. We considered the exposure to be ipsilateral if the phone was used predominantly on the same side as the tumor or on both sides of the head. We considered the exposure to be contralateral if the phone was used mostly on the side of the head opposite to the tumor. No laterality was assigned if the tumor was centrally located, and separate analyses were made with these subjects.

We also analyzed the potential relationship between other sources of radio frequency exposure and the risk for brain tumors. Specifically, we analyzed whether subjects ever used baby monitors near the head, ever used cordless phones, and the cumulative duration and number of calls with cordless phones in the first 3 years of use.

The software Stata/SE, version 10.1 (StataCorp, College Station, TX), was used for all analyses (22).

Time Trend Analysis

Because usage of mobile phones among children and adolescents has been a relatively recent and rapidly increasing phenomenon, we compared our study results with the observed time trends of brain tumor incidence. Most recent incidence data from among the four participating countries were available from Sweden (http://www.socialstyrelsen.se/statistik/statistikdatabas; accessed May 27, 2011). We used the observed brain tumor incidence data of Swedish children and adolescents aged 5–19 years from 1990 to 2008 and added hypothetical incidence rate trends derived from our risk estimates for regular mobile phone use based on self-reported and operator recorded data and estimated exposure prevalence (23). The proportion of regular mobile phone users was estimated by combining data from the control subjects in CEFALO with subscriber data in Sweden (http://www.itu.int/ITU-D/ict/; accessed May 27, 2011).

Results

In total, 423 case patients and 909 potential control subjects were identified during the study period. Interviews were completed with 352 (83.2%) eligible case patients and 646 (71.1%) eligible control subjects. The participation rates among case patients ranged from 65.7% in Norway to 97.7% in Denmark and among control subjects from 58.2% in Norway to 76.3% in Sweden. The main reasons for nonparticipation were refusal to participate (18 case patients and 172 control subjects), inability to contact the subject (five case patients and 70 control subjects), and physicians' denial of permission to contact some patients due to the severity of their disease (19 case patients). The median age of the study participants overall was 13 years and 46% were female (Table 1).

Among the 352 case patients, 162 (46.0%) were diagnosed with an astrocytoma, 21 (6.0%) with ependymoma, 30 (8.5%) with another glioma, 62 (17.6%) with primitive neuroectodermal tumors, 53 (15.1%) with other specified intracranial neoplasms, and 24 (6.8%) with unspecified intracranial neoplasms.

Use of Mobile Phones

There were 265 (75.3%) case patients and 466 control subjects (72.1%) who reported having spoken on a mobile phone more than 20 times before the time when the case patient was diagnosed. Regular mobile phone use was reported by 194 (55%) case patients

Table 1. Characteristics of case patients and control subjects

Characteristic	Case patients (n = 352) No. (%)	Control subjects (n = 646) No. (%)
Country		
Denmark	85 (24.1)	170 (26.3)
Sweden	138 (39.2)	228 (35.3)
Norway	44 (12.5)	78 (12.1)
Switzerland	85 (24.1)	170 (26.3)
Age at reference date, y*		
7–9	88 (25.0)	167 (25.9)
10–14	144 (40.9)	265 (41.0)
15–19	120 (34.1)	214 (33.1)
Sex		
Female	162 (46.0)	293 (45.4)
Male	190 (54.0)	353 (54.6)
Highest educational level of parents†		
Low	20 (5.7)	26 (4.0)
Intermediate	188 (53.4)	336 (52.0)
High	144 (40.9)	279 (43.2)
Unknown	0 (0)	5 (0.8)

* Age at diagnosis for case patients and matched control subjects.

† Low: elementary school not completed; intermediate: elementary school, high school, or apprenticeship; high: university or technical college.

and 329 (51%) control subjects. Brain tumor patients were not statistically significantly more often regular mobile phone users compared with control subjects (OR = 1.36; 95% CI = 0.92 to 2.02; Table 2). We also looked at various other exposure surrogates and observed somewhat elevated odds ratios without a clear exposure–response relationship for the following exposure variables: time since first use (P_{trend} = .37), cumulative duration of subscriptions (P_{trend} = .14), cumulative duration of calls (P_{trend} = .42), and cumulative number of calls (P_{trend} = .58). Children who started to use mobile phones at least 5 years ago were not at increased risk compared with those who had never regularly used mobile phones (OR = 1.26, 95% CI = 0.70 to 2.28; Table 2).

For regular use of mobile phones, a stratified analysis by country yielded odds ratios greater than 1 for all countries except Norway (Table 3), although the observed pattern was in line with random variability (*P* for heterogeneity = .20). In stratified analyses according to age at diagnosis (<15 and ≥15 years), sex, tumor location, tumor morphology, and time difference between case and control interviews, the odds ratios of regular use of mobile phones were not statistically significantly different between the strata.

We found no elevated risk among regular users of mobile phones when we looked at the parts of the brain with the highest radio frequency exposure, that is, the temporal and frontal lobes and the cerebellum (Table 3). On the other hand, we did find a statistically significant odds ratio for tumors in the parts of the brain with the lowest exposure to radiation among regular users of mobile phones (OR = 1.92; 95% CI = 1.07 to 3.44).

Operator Recorded Data

To confirm the results that we obtained from questionnaires, we also analyzed data on phone use, when available, from the mobile phone companies. Operator recorded data regarding the amount of time that had elapsed since the phone users' first subscriptions were activated were available for 35% of case patients and 34% of control subjects who reported to have a mobile phone subscription. For this subset of subjects, we found a statistically significantly increased risk among users with the longest period since first subscription (OR = 2.15 [95% CI = 1.07 to 4.29] among 24 case patients and 25 control subjects who had subscriptions for more than 2.8 years, P_{trend} < .001; Table 4). We also tabulated records for cumulative duration of subscription, cumulative hours of use, and cumulative number of calls. For each of these categories, exposure–response trends were not statistically significant. Risk estimates based on self-reported data were similar for the subset of subjects for whom operator data were available compared with the corresponding risk estimates in the subset with no operator data.

Laterality of Mobile Phone Use

Because the absorbance of radiation from a mobile phone is highly localized to the side of the head where the phone is held, we also examined laterality of mobile phone use and occurrence of brain tumors. The odds ratio for brain tumor risk among ipsilateral regular users of mobile phones was not higher than the odds ratio of contralateral regular users (OR = 1.74, 95% CI = 0.91 to 3.33 and

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) of brain tumors associated with mobile phone use*

Variable	Case patients, No.	Control subjects, No.	OR (95% CI)	P_{trend}†
Regular use‡				
No§	158	317	1.0 (referent)	
Yes	194	329	1.36 (0.92 to 2.02)	
Time since first use, y				.37
Never regular user	158	317	1.0 (referent)	
≤3.3	95	165	1.35 (0.89 to 2.04)	
3.3–5.0	53	83	1.47 (0.87 to 2.49)	
>5.0	46	81	1.26 (0.70 to 2.28)	
Cumulative duration of subscriptions, y§				.14
Never regular user	158	317	1.0 (referent)	
≤2.7	94	163	1.34 (0.89 to 2.01)	
2.8–4.0	45	78	1.45 (0.83 to 2.54)	
>4.0	52	81	1.58 (0.86 to 2.91)	
Cumulative duration of calls, h§				.42
Never regular user	158	317	1.0 (referent)	
≤35	94	162	1.33 (0.89 to 2.01)	
36–144	48	81	1.44 (0.85 to 2.44)	
>144	49	81	1.55 (0.86 to 2.82)	
Cumulative number of calls§				.58
Never regular user	158	317	1.0 (referent)	
≤936	94	163	1.34 (0.89 to 2.02)	
937–2638	50	80	1.47 (0.86 to 2.51)	
>2638	47	79	1.42 (0.79 to 2.53)	

* Mobile phone use was defined as regular use, time since first use, cumulative duration of subscriptions, cumulative duration of calls, and cumulative number of calls.

† *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

‡ "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

§ Six observations were dropped from the analysis because four participants had missing exposure data.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for stratified analyses

	Regular use*					
	No†			Yes		
Stratum	Case patients n	Control subjects n	OR (95% CI)	Case patients n	Control subjects n	OR (95% CI)
Main analysis (for comparison)	158	317	1.0 (referent)	194	329	1.36 (0.92 to 2.02)
By country						
Denmark	36	78	1.0 (referent)	49	92	1.49 (0.61 to 3.61)
Sweden	57	109	1.0 (referent)	81	119	1.73 (0.87 to 3.41)
Norway	21	31	1.0 (referent)	23	47	0.51 (0.18 to 1.41)
Switzerland	44	99	1.0 (referent)	41	71	1.69 (0.79 to 3.61)
By age-group, y‡						
<15	146	292	1.0 (referent)	86	140	1.42 (0.89 to 2.26)
≥15	12	25	1.0 (referent)	108	189	1.23 (0.59 to 2.58)
By sex						
Female	61	123	1.0 (referent)	101	170	1.52 (0.81 to 2.84)
Male	97	194	1.0 (referent)	93	158	1.27 (0.76 to 2.11)
By time between diagnosis and interview, y§						
≥1.5	122	257	1.0 (referent)	133	244	1.10 (0.75 to 1.61)
<1.5	35	60	1.0 (referent)	61	85	1.53 (0.68 to 3.43)
By time between cases' and controls' interviews						
Both controls within 50 d	69	151	1.0 (referent)	89	165	1.46 (0.81 to 2.62)
One or more controls >50 d	89	166	1.0 (referent)	105	164	1.29 (0.75 to 2.20)
By tumor location						
Temporal, frontal lobes, and cerebellum	83	155	1.0 (referent)	98	178	1.00 (0.58 to 1.72)
Other than temporal, frontal lobes, and cerebellum	75	162	1.0 (referent)	96	151	1.92 (1.07 to 3.44)
By tumor morphology						
Astrocytoma and other glioma	84	160	1.0 (referent)	108	189	1.14 (0.66 to 1.97)
All except astrocytomas and other glioma	74	157	1.0 (referent)	86	140	1.65 (0.93 to 2.93)
By latency time, y						
2	222	436	1.0 (referent)	130	210	1.34 (0.90 to 1.99)
5	319	601	1.0 (referent)	33	45	1.36 (0.77 to 2.40)

* "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

† Reference category.

‡ Age of patients at diagnosis and comparable age for matched control subjects.

§ Based on unconditional logistic regression adjusted for geographical region, sex, and age.

OR = 2.07, 95% CI = 0.95 to 4.52, respectively; Table 5). For all exposure surrogates except time since first use of mobile phones, odds ratios of contralateral use in the highest exposure category were larger than the odds ratios for ipsilateral use. For those excluded from the laterality inverse exposure–response associations were observed.

Other Radio Frequency Electromagnetic Field Exposure Sources

We also evaluated other potentially relevant sources of radio frequency electromagnetic fields in early life. We found no evidence for a relationship between ever use of baby monitors near the head and brain tumor risk (OR = 0.96, 95% CI = 0.50 to 1.86; Table 6). In addition, children's use of cordless phones was not related to brain tumor risk (for the group with the highest amount of cordless phone use [>70 hours], OR = 1.18, 95% CI = 0.65 to 2.14; Table 6).

Evaluation of Time Trends

We also examined the age-adjusted brain tumor incidence rates among Swedish children and adolescents aged 5–19 years from 1990 to 2008 including hypothetical incidence rate trends (Figure 1). In these estimates, we made the assumption that regular use of mobile phones increases the risk of brain tumors by 36% (based on self-reported exposure; Table 2) or 115% after 3 years of regular mobile phone use (based on operator recorded exposure; Table 4). A risk estimate of 2.15 after 3 years of regular mobile phone use is expected to increase the incidence rate by about 50% in the last 10 years based on the proportion of regular users in our study collective. No such trend was observed in the incidence rates; in fact, rather the opposite trend was observed. This indicates that short-term use of mobile phone does not cause brain tumors in children and adolescents.

Discussion

The CEFALO study is the first case–control study of use of mobile phones and brain tumor risk in children and adolescents to our knowledge. Our primary analysis does not point to a statistically significantly increased risk for brain tumors in children that is associated with the use of mobile phones. There was no consistent exposure–response relationship either in terms of the amount of mobile phone use or by the location of the tumor. In a small subset of study participants with operator recorded data (n = 163),

Table 4. Comparison of analyses with operator-recorded and self-reported mobile phone use

	Operator recorded use				Self-reported use in collective with available operator data				Self-reported use in collective without available operator data			
Variable	Case patients n	Control subjects n	OR (95% CI)	P_{trend}*	Case patients n	Control subjects n	OR (95% CI)	P_{trend}*	Case patients n	Control subjects n	OR (95% CI)	P_{trend}*
Time since first subscription, y				.001				.25				.22
Never regular user†	134	259	1.0 (referent)		127	245	1.0 (referent)		154	305	1.0 (referent)	
≤1.8	19	51	0.78 (0.43 to 1.40)		33	62	1.09 (0.65 to 1.84)		59	103	1.17 (0.79 to 1.74)	
1.8–2.8	19	25	1.71 (0.85 to 3.44)		17	25	1.47 (0.69 to 3.14)		30	57	1.15 (0.67 to 1.97)	
>2.8	24	25	2.15 (1.07 to 4.29)		19	28	1.51 (0.68 to 3.35)		36	54	1.47 (0.81 to 2.67)	
Cumulative duration of subscriptions, y				.15				.62				.18
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤1.8	13	26	1.14 (0.55 to 2.37)		21	36	1.24 (0.66 to 2.33)		73	128	1.19 (0.82 to 1.72)	
1.9–3.3	10	13	1.73 (0.71 to 4.20)		8	15	1.17 (0.44 to 3.13)		37	67	1.23 (0.74 to 2.05)	
>3.3	11	13	1.84 (0.74 to 4.58)		12	21	1.19 (0.47 to 3.03)		40	61	1.46 (0.83 to 2.55)	
Cumulative duration of calls, h				.36				.85				.47
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤11	14	26	1.24 (0.61 to 2.55)		23	34	1.50 (0.79 to 2.83)		71	130	1.14 (0.79 to 1.65)	
12–27	11	13	1.95 (0.81 to 4.73)		7	21	0.70 (0.27 to 1.81)		41	61	1.48 (0.89 to 2.47)	
>27	9	13	1.38 (0.53 to 3.61)		11	17	1.27 (0.46 to 3.49)		38	65	1.36 (0.77 to 2.40)	
Cumulative number of calls				.60				.74				.57
Never regular user†	133	259	1.0 (referent)		125	239	1.0 (referent)		155	311	1.0 (referent)	
≤573	16	26	1.43 (0.71 to 2.88)		21	32	1.51 (0.78 to 2.92)		73	132	1.15 (0.79 to 1.66)	
574–1292	11	13	1.79 (0.74 to 4.29)		8	21	0.71 (0.28 to 1.79)		42	61	1.51 (0.91 to 2.51)	
>1292	7	13	1.08 (0.38 to 3.06)		12	19	1.34 (0.53 to 3.35)		35	63	1.24 (0.71 to 2.16)	

* *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

† Reference category (among never regular users, 123 cases and 233 control subjects reported to have no subscription and were included as references in all analyses).

Table 5. Association between brain tumors and mobile phone use by side of phone use*

Variable	Ipsilateral use				Contralateral use				Central or unknown location			
	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†	Case patients n	Control subjects n	OR (95% CI)	P_{trend}†
Regular use‡												
No	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
Yes	62	83	1.74 (0.91 to 3.33)		49	63	2.07 (0.95 to 4.52)		68	135	0.74 (0.40 to 1.39)	
Time since first use, y				.08				.08				.08
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤3.3	29	40	1.73 (0.87 to 3.44)		24	36	1.86 (0.82 to 4.21)		36	68	0.81 (0.41 to 1.57)	
3.3–5.0	15	25	1.53 (0.62 to 3.76)		16	16	3.27 (1.10 to 9.68)		19	31	0.82 (0.34 to 1.94)	
>5.0	18	18	2.75 (0.93 to 8.06)		9	11	2.39 (0.67 to 8.57)		13	36	0.36 (0.13 to 1.02)	
Cumulative duration of subscriptions, y				.02				.03				.01
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤2.7	28	44	1.54 (0.78 to 3.05)		23	35	1.83 (0.81 to 4.15)		37	60	0.90 (0.48 to 1.69)	
2.8–4.0	14	19	2.38 (0.84 to 6.80)		13	17	2.67 (0.88 to 8.11)		15	32	0.44 (0.17 to 1.15)	
>4.0	20	20	3.74 (1.19 to 11.77)		12	9	4.00 (1.11 to 14.41)		15	40	0.23 (0.07 to 0.74)	
Cumulative duration of calls, h				.14				.03				.02
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤35	28	48	1.46 (0.74 to 2.91)		19	35	1.65 (0.73 to 3.74)		40	59	0.97 (0.50 to 1.85)	
36–144	17	17	2.66 (1.05 to 6.71)		13	17	4.14 (1.25 to 13.66)		15	37	0.43 (0.18 to 1.03)	
>144	17	18	2.64 (0.92 to 7.59)		16	9	6.19 (1.57 to 24.35)		12	36	0.24 (0.08 to 0.73)	
Cumulative number of calls				.08				.06				.02
Never regular user	146	267	1.0 (referent)		141	257	1.0 (referent)		147	257	1.0 (referent)	
≤936	30	46	1.59 (0.81 to 3.12)		22	38	1.74 (0.78 to 3.90)		37	57	0.98 (0.51 to 1.92)	
937–2638	13	19	2.06 (0.72 to 5.93)		14	12	5.37 (1.54 to 18.72)		17	38	0.54 (0.24 to 1.23)	
>2638	19	18	2.91 (1.09 to 7.76)		12	11	4.82 (1.21 to 19.24)		13	37	0.31 (0.11 to 0.87)	

* All matched sets in which the case patient and/or the control subject was a regular contralateral user were excluded from the ipsilateral analyses; similarly, sets in which the case patient and/or the control subject was a regular ipsilateral user were excluded from the contralateral analyses. CI = confidence intervals; OR, odds ratio.

† *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

‡ "Regular use" was defined as use of a mobile phone at least once per week for a period of 6 months or more.

Table 6. Odds ratios (ORs) and 95% confidence intervals (CIs) of brain tumors associated with other radio frequency electromagnetic field exposure sources*

Variable	Case patients No.	Control subjects No.	OR (95% CI)	P_{trend}*
Ever use of baby monitors† near the head				
No	335	611	1.0 (referent)	
Yes	17	35	0.96 (0.50 to 1.86)	
Ever use of cordless phones				
No	110	216	1.0 (referent)	
Yes	242	430	1.09 (0.81 to 1.45)	
Cumulative duration of calls with cordless phones, h‡				.20
Never user of cordless phones	102	189	1.0 (referent	
≤23	70	135	0.98 (0.65 to 1.46)	
24–70	39	60	1.15 (0.71 to 1.87)	
>70	25	38	1.18 (0.65 to 2.14)	
Missing	116	224	0.94 (0.67 to 1.32)	
Cumulative number of calls with cordless phones‡,§				.20
Never user of cordless phones	102	189	1.0 (referent)	
≤235	61	116	1.01 (0.66 to 1.53)	
236–704	48	79	1.07 (0.68 to 1.69)	
>704	27	39	1.21 (0.68 to 2.15)	
Missing	114	223	0.94 (0.67 to 1.31)	

* *P* values for tests of trend were calculated by means of a two-sided Wald test for regression models in which exposure was included as continuous variable, and all subjects in a category were assigned the median value of their corresponding category.

† Wireless baby monitor or alarm to remotely listen to sounds made by an infant.

‡ In the first 3 years of use.

§ The 75th and 90th percentiles served as cutoffs because of broad categories.

however, time since the start of a mobile phone subscription was statistically significantly related to brain tumor risk.

Because of the methodological limitations of retrospective case–control studies and the absence of a known biological mechanism for carcinogenicity by low-dose microwave radiation, we considered several measures of exposure and conducted various stratified and sensitivity analyses to evaluate the consistency of our findings. Most results of these analyses were in line with the primary analysis and did not indicate an increased risk. However, we did observe a statistically significant trend of increasing risk with increasing time since first subscription when we used the data recorded by the network operators (Table 4). There was no

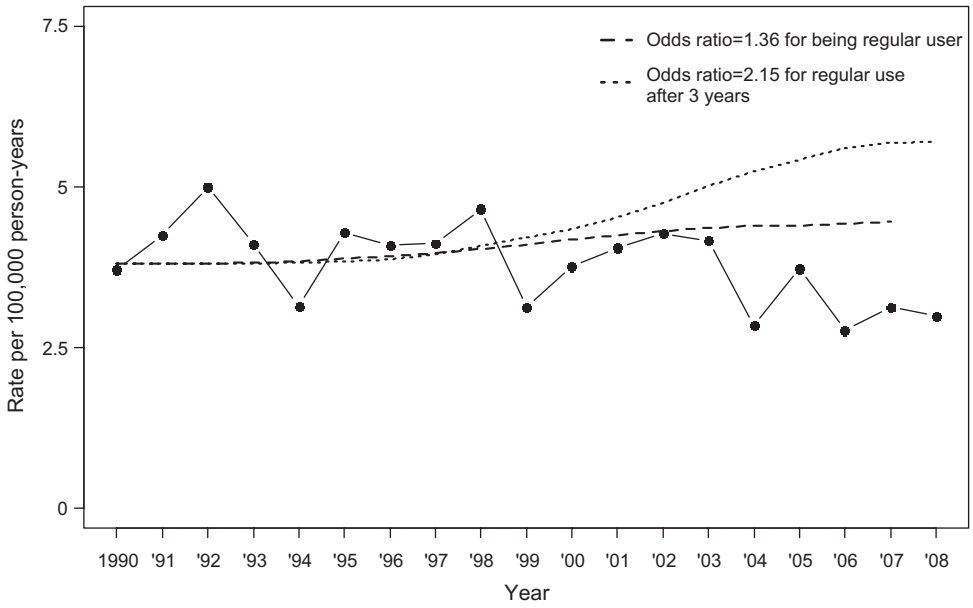

Figure 1. Gender and age-standardized incidence rates among Swedish children and adolescents aged 5–19 years between 1990 and 2008 (solid line). **Dotted lines** denote hypothetical incidence rate trends under the assumption that regular use of mobile phones increases the risk for brain tumors by 36% (odds ratio [OR] = 1.36) (without considering a latency period) and by 115% (OR = 2.15) after 3 years of regular mobile phone use (based on risk estimates in Tables 2 and 4), respectively.

consistent trend with cumulative duration or number of calls. Operator recorded data are considered more reliable and less prone to recall bias than self-reported exposure data. However, our data were limited because we obtained operator recorded time since first subscription from only 35% of case patients and 34% of control subjects who reported to own a subscription. These proportions were even smaller for the other operator recorded exposure surrogates. In addition, operator data themselves have limitations. For example, the children had to remember their phone number(s) for us to be able to link to the operator data, and we still had to rely on interviews to account for whether recorded calls were made or taken with the use of hands-free devices. Also, we could obviously not verify from operator data whether the children themselves or others were using the mobile phone for any given recorded call. It is quite likely that the child occasionally lent out his or her phone to a peer or, in contrast, borrowed a phone from someone else. For underage study participants, subscriptions were sometimes held in the name of the parents and disentangling of the actual user(s) of each subscription may sometimes have been erroneous.

Reverse causality is another aspect to consider when interpreting the observed increased risk for time since first subscription. Reverse causality exists if the condition of having a brain tumor itself prompted the use of mobile phones and thus the exposure of interest. For example, because of prodromal symptoms before diagnosis, some case patients may have appeared frailer than healthy children (24,25). To provide frail children better protection, parents may have given them a mobile phone to use in case of emergency or to keep in contact with friends in a situation with reduced mobility.

To estimate recall bias, we compared self-reported and objective mobile phone use data (26). We found that the duration and number of calls were overestimated by case patients (median ratio = 1.09, interquartile range [IQR] = 0.47–2.27 for number of calls and median ratio = 1.52, IQR = 0.63–4.28 for duration of calls) and control subjects (median ratio = 1.34, IQR = 0.63–5.36 for number of calls and median ratio = 2.63, IQR = 0.89–10.06 for duration of calls). The average extent of overestimation was not statistically significantly different between case patients and control subjects, suggesting that there was no substantial recall bias; however, the confidence limits were wide.

Because we did not find a clear exposure–response relationship in most of these analyses, the available evidence does not support a causal association between the use of mobile phone and brain tumors. Furthermore, some results of our sensitivity analyses make a causal relationship appear to be unlikely. For instance, odds ratios for brain tumors in analyses restricted to case patients with tumors in the temporal and frontal lobes and the cerebellum were not increased compared with odds ratios from the corresponding main analyses. If there was a causal relationship, we would expect an increased risk specifically in these regions because the absorption of radio frequency energy from mobile phones is highly localized and has been shown to be considerably higher in the temporal and frontal lobes and the cerebellum compared with other parts of the brain (27). In fact, in laterality analyses, we found a higher risk for contralateral tumors than for ipsilateral tumors relative to where mobile phones were held and even found fewer tumors with a central or an unknown location, whereas if a causal relationship existed, highest risk for ipsilateral tumors would be expected (28). However, the number of participants in this analysis was small and confidence intervals were large. In addition, subjects' statements about which side of the head they preferred to hold the mobile phone near during its use are often considered unreliable as was discussed in the INTERPHONE study (13).

Hardell and colleagues [eg, (15)] consistently found estimates of brain tumor risk to be of the same order of magnitude for both uses of mobile and cordless phones. In this study, however, we found no statistically significantly increased risk for brain tumors in relation to cordless phone use.

Our study has several strengths. Participation rates were high for case patients (83.2%) and for control subjects (71.1%) compared with other case–control studies on mobile phone use and brain tumors in adults (13). Most importantly, when we used a logistic regression model to analyze the nonresponder interviews of control subjects by assessing the participation probabilities of users and nonusers of mobile phones, we did not find that the probability of participation was different between mobile phone users and nonusers according to case or control status [data not shown, see (26) for details]. Thus, the occurrence of relevant selection bias is unlikely in the CEFALO study.

To assess the possibility of confounding, we collected information on the socioeconomic status of the parents, past radiation exposure, family history of cancer, animal contact, maternal smoking during pregnancy, and information about where the child lived until the age of 6 years. None of these potential confounders led to a noticeable change in the risk estimates. However, little is known about the etiology of childhood brain tumors. Apart from some rare genetic factors and high doses of ionizing radiation, no other risk factors have yet been established (29,30). Nevertheless, it cannot be excluded that we missed some potentially but still unknown relevant risk factors or confounders.

Our study also has limitations. We recruited case patients during a 4-year period in four countries. We chose the age range of the participants to maximize the probability of exposure to mobile phones. Nevertheless, because childhood brain tumors are rare (30), we could eventually include only 352 case patients and about two control subjects for each patient. Thus, the statistical power of the study to detect small risk increases was limited. In addition, we carried out multiple tests and some statistically significant results can be expected by pure chance underlining our cautious interpretation of the few positive findings.

There might also be an inherent limitation regarding the level of exposure in our study. Use of mobile phones is common among adolescents and children, and it is possible that the amount of use has increased since CEFALO was carried out. For example, 8% of participants aged 12–15 years at the time of diagnosis were already regular mobile phone users at the age of 10, whereas this was true for only 2% of participants aged 16–19 years at the time of diagnosis. Notably, most participants in our study used Global System for Mobile Communication (GSM) type mobile phones, whereas use of Universal Mobile Telecommunications System (UMTS) phones is becoming more popular and widespread nowadays. Recent studies have demonstrated that the average output power

of UMTS phones is 100–500 times lower than that of a typical GSM phones during average use (31,32). Thus, the actual time-weighted exposure of the brain to radio frequency radiation may even have decreased in more recent years despite the increased use of mobile phones.

A recent study (33) that investigated the incidence of malignant and benign childhood central nervous system neoplasms in the Nordic countries found that the incidence rates of brain tumors in children aged 0–14 years remained stable at a high level during the last 22 years and concluded that major changes in environmental risk factors are unlikely. The same study, however, found a statistically significant increase in incidence of 1.02% per year for children aged 10–14 years. In England, no increase in the brain tumor incidence was observed between 1998 and 2007 among adolescents aged 10–20 years (33). Furthermore, a study that analyzed the brain cancer incidence trends in the United States reported stable time trends from 1992 to 2006 for both boys and girls who were younger than 20 years (34). These data are in line with our evaluation of time trends of brain tumor incidence in Sweden and altogether provide little support to the view that mobile phone use increases the risk of brain tumors.

In summary, we did not observe that regular use of a mobile phone increased the risk for brain tumors in children and adolescents. However, in a small subset of study participants for whom operator recorded data was available, brain tumor risk was related to the time elapsed since the start of their mobile phone subscriptions but was not related to the amount of use. The lack of an exposure–response relationship, given our finding that risk was related to neither the amount of mobile phone use and nor the location of the tumor, does not support a causal interpretation. Moreover, brain tumor incidence in Sweden has not increased among children and adolescents in the last few years. We cannot, however, rule out the possibility that mobile phones confer a small increase in risk and therefore emphasize the importance of future studies with objective exposure assessment or the use of prospectively collected exposure data. We doubt that further retrospective studies based mainly on recall will contribute to clarification. We also recommend rigorous joint efforts of population-based cancer registries to monitor time trends in incidence rates including collection of complete diagnostic data such as tumor topography, morphology, and laterality for at least the majority of patients. Because use of mobile phones has become very common among children and adolescents in most countries worldwide, even a small risk increase should be reflected in future incidence rate trends.

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