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Wireless phone use in childhood and adolescence and neuroepithelial brain tumours: Results from the international MOBI-Kids study

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Abbreviations: BT, brain tumour; CI, confidence interval; CICD, cumulative induced current density; COG, centre of gravity; CSE, cumulative specific energy; DECT, digital enhanced cordless telecommunications; ELF, extremely low frequency; EMF, electromagnetic fields; IARC, International Agency for Research on Cancer; ICD-O, International Classification of Diseases for Oncology; MRI, magnetic resonance imaging; NBT, neuro-epithelial brain tumours; OR, odds ratio; RF, radiofrequency electromagnetic fields; VoIP, Voice over Internet Protocol; WHO, World Health Organisation; Wi-Fi, Wireless Fidelity.

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ABSTRACT

In recent decades, the possibility that use of mobile communicating devices, particularly wireless (mobile and cordless) phones, may increase brain tumour risk, has been a concern, particularly given the considerable increase in their use by young people. MOBI-Kids, a 14-country (Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, the Netherlands, New Zealand, Spain) case-control study, was conducted to evaluate whether wireless phone use (and particularly resulting exposure to radiofrequency (RF) and extremely low frequency (ELF) electromagnetic fields (EMF)) increases risk of brain tumours in young people. Between 2010 and 2015, the study recruited 899 people with brain tumours aged 10 to 24 years old and 1,910 controls (operated for appendicitis) matched to the cases on date of diagnosis, study region and age. Participation rates were 72% for cases and 54% for controls.

The mean ages of cases and controls were 16.5 and 16.6 years, respectively; 57% were males. The vast majority of study participants were wireless phones users, even in the youngest age group, and the study included substantial numbers of long-term (over 10 years) users: 22% overall, 51% in the 20–24-year-olds.

Most tumours were of the neuroepithelial type (NBT; n = 671), mainly glioma. The odds ratios (OR) of NBT appeared to decrease with increasing time since start of use of wireless phones, cumulative number of calls and cumulative call time, particularly in the 15–19 years old age group. A decreasing trend in ORs was also observed with increasing estimated cumulative RF specific energy and ELF induced current density at the location of the tumour.

Further analyses suggest that the large number of ORs below 1 in this study is unlikely to represent an unknown causal preventive effect of mobile phone exposure: they can be at least partially explained by differential recall by proxies and prodromal symptoms affecting phone use before diagnosis of the cases. We cannot rule out, however, residual confounding from sources we did not measure.

Overall, our study provides no evidence of a causal association between wireless phone use and brain tumours in young people. However, the sources of bias summarised above prevent us from ruling out a small increased risk.

1. Introduction

Mobile phone ownership and use has increased substantially in recent decades in all age groups of people. Worldwide, the number of mobile phone subscriptions almost doubled in the decade 2008–2018, from 4,1 to 7,9 billion subscribers overall (Statista, 2021), corresponding to about 104 mobile phone subscriptions per 100 inhabitants. The increase was particularly apparent among children and adolescents. In the UK, 96% of young people between 16 and 24 years of age report owning a smartphone since 2017 (Statista UK, 2021), compared to 66% in 2012. In Korea, 87.2% of children aged 9 to 11 years reported owning a smart phone in 2011, compared to 55.3% in 2008 (Byun et al., 2013). In Germany, over 80% of 12–19-year-olds used a smartphone by 2015, compared to 25% in 2011 (Statista Germany, 2021).

Wireless phones – both mobile and cordless phones – are a source of exposure to electromagnetic fields (EMF), in particular radiofrequency fields (RF) used for communications (IARC, 2013) and extremely low frequency (ELF) electromagnetic fields (Calderón et al., 2014). Both ELF and RF have been classified as possibly carcinogenic to humans (group 2B) by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) (IARC, 2013, 2002). The RF evaluation was based on limited evidence of carcinogenicity in humans (positive associations were reported between exposure to RF from wireless phones and risk of glioma and acoustic neuroma in adults) and in experimental animals (Baan et al., 2011). The ELF evaluation was based on limited evidence of carcinogenicity in humans (associations between ELF magnetic fields and childhood leukaemia) and inadequate evidence in experimental animals (IARC, 2002). The human evidence for ELF and brain tumours was judged to be inadequate.

Most studies of cancer risk from mobile phones have focused on brain tumours (BT), as the brain is the tissue which most absorbs RF energy emitted by mobile phones when they are held close to the head. Numerous analyses of time trends in brain tumours have been conducted in the last 15 years (Chapman et al., 2016; Choi et al., 2021; Davis et al., 2020; de Vocht, 2019, 2016; de Vocht et al., 2011; Deltour et al., 2009; GBD 2016 Brain and Other CNS Cancer Collaborators, 2019; Hardell and Carlberg, 2017, 2015a; Karipidis et al., 2018; Keinan-Boker et al., 2018; Little et al., 2012; Lonn et al., 2004; Philips et al., 2018; Sato et al., 2016; Voisin et al., 2021; Zada et al., 2012). Globally, the age-standardised incidence rates of brain and CNS cancer tumours has increased by about 17·3% between 1990 and 2016 (GBD 2016 Brain and Other CNS Cancer Collaborators, 2019), with important geographical variations. An important part of this increase is thought to be related to diagnostic improvements and changes in diagnostic classifications. Several studies have reported increases in the incidence of high grade tumours and/or tumours in specific anatomic locations, in particular the frontal and temporal lobe (de Vocht, 2016; Philips et al., 2018; Zada et al., 2012) and postulated these might be related to the use of mobile phones in the population. Further analyses and comparisons across countries and age groups suggest these may reflect improved data collection practices in surveillance systems, in particular at older ages, making any inference about possible effects of mobile phones difficult (Chapman et al., 2016;

Davis et al., 2020; de Vocht, 2019; Hardell and Carlberg, 2017). Studies of time trends in young people are likely to be less prone to diagnostic uncertainties, but few studies are available. In Canada, no increase in paediatric brain tumours has been observed between 1992 and 2017 (Voisin et al., 2021).

Analyses of large-scale cohort studies (Benson et al., 2013; Frei et al., 2011) have not shown an association between mobile phone use and BT risk. Despite large sample sizes, these studies have little power to rule out weak associations as the number of BT cases in long-term users remains small and the studies are subject to substantial exposure misclassification (Ahlbom et al., 2007; IARC, 2013).

Research on BT risk in relation to mobile phone use presents major methodological challenges (E. Cardis et al., 2011; Cardis and Sadetzki, 2011; Sadetzki et al., 2014), in particular the important skewness of the exposure distribution and the fact that RF dose from mobile phones has been shown to be very localized, with most of the energy being absorbed in the outer layers of the temporal lobe in adults and decreasing rapidly with increasing depth (Cardis et al., 2008). Therefore, any increased risk related to EMF from mobile phones may affect only a small proportion of the brain and hence a small proportion of cases.

Carefully designed epidemiological studies with detailed mobile phone history and sufficient numbers of cases of the relatively rare outcome of interest (here BTs) are needed to adequately evaluate potential risks. Up to now, collection of detailed mobile phone history has only been possible in case-control studies. Though they are subject to limitations such as recall bias, large-scale case-control studies in the last decade have suggested a possible association between mobile phone use (and RF energy absorption in the brain) and risk of brain and CNS tumours. These findings are the basis for the IARC Monographs RF evaluation (Baan et al., 2011).

The largest of these case-controls studies, the INTERPHONE study, included a total of 2,708 glioma, 2,409 meningioma and 1,104 acoustic neuroma cases and their respective controls from 13 countries (INTERPHONE Study Group, 2011, 2010). For all three tumour types, the vast majority of ORs related to levels of mobile phone use were below one, possibly due to selection bias or other methodological limitations (Cardis and Sadetzki, 2011). Increased ORs for glioma and acoustic neuroma were, however, found in the highest decile ($\geq$1640 h) of lifetime use, with no evidence of a dose–response relationship. The OR was largest for tumours on the side of the head where the phone was reported to be used and, for glioma, for tumours in the temporal lobe, where RF dose is highest. Use of a probabilistic multiple-bias model to simultaneously adjust for potential selection bias and recall error had little effect on the risk estimates in the Canadian INTERPHONE data set (Momoli et al., 2017). Analyses of risk in relation to estimates of RF energy deposition at the tumour location in a subset of INTERPHONE countries showed a dose-related increased risk of glioma among the longest users (7 years or more) (E. Cardis et al., 2011), suggesting a possible effect of RF. No association was seen between amount of phone use and distance from the tumour to the mobile phone axis in a case-case analysis in another subset of INTERPHONE countries, though an OR of 2 (95% CI 0.68, 5.85) was observed among long term users (10 years or more) for tumours with midpoint 5 cm or less from the mobile phone axis in a case-specular analysis, based on a small number of cases (Larjavaara et al., 2011). Further analyses of the entire INTERPHONE dataset showed an association between the intracranial distribution of gliomas and self-reported location of the phone, which, however, was independent of the amount of phone use (Grell et al., 2016).

In Sweden, Hardell and collaborators conducted several large-scale case-control studies of BTs in relation to mobile phone use. In a pooled analysis of glioma (Hardell and Carlberg, 2015b) including 1,498 cases and 3,530 controls an OR of 1.3 (95% CI 1.1–1.6) was reported for ever use of a wireless phone. The OR was higher among those who started using phones 15 years or more in the past (ranging from 1.7 to 3 among those who started use 15–20, 20–25 and 25 years or more in the past). The ORs increased with increasing cumulative use of phones, with an OR of 2.0 (95% CI 1.6–2.6) among those in the highest quartile of reported use (over 1486 h of use). The OR was highest among those who started before the age of 20, for ipsilateral use and for tumours in the temporal lobe. A case-control study in France also reported increased ORs for glioma and meningioma among heaviest mobile phone users, with higher ORs for tumours in the temporal lobe (Coureau et al., 2014).

None of the studies published to date evaluated the possible effect of ELF from mobile phones on BT risk, but the possible association between ELF and brain tumour risk has been studied in residential and occupational settings. Studies of brain tumour risk in children from residential ELF exposures have been recently reviewed and a meta-analysis conducted (Seomun et al., 2021). Numbers of exposed cases were very small in each study, with a total of 28 and 10 cases with exposure levels above 0.2-μT and 0.4-μT, respectively. Estimated ORs were 0.95 (95% CI 0.59–1.56) and 1.25 (95% CI 0.93–1.61), respectively at these two exposure levels. Studies of the effects of exposure on risk of adult brain tumours are mixed, with a meta-analysis of occupational studies reporting an 18% increase in the risk of glioma for higher ELF exposure levels (Kheifets et al., 2008), with no clear pattern of risk, and conflicting results in relation to residential ELF exposure (Baldi et al., 2011; Carles et al., 2020; Elliott et al., 2013; Khan et al., 2021; Marcilio et al., 2011).

With the considerable increase in use in children and adolescents in the last 15 years, an important question is the possible effect of mobile phones on BTs in young people. This is particularly important given that, if a risk exists, it may be greater for exposures at younger ages due to ongoing brain development. Furthermore, children who start using phones will have many more years of exposure to RF and ELF fields from communication devices than those who started as adults and, for RF at least, the most exposed parts of the brain may receive higher exposure when calling in children than in adults (Wiart et al., 2008).

To date, only one study (CEFALO) of BT risk in relation to mobile phone use in young people has been published (Aydin et al., 2011). This study, which included 352 cases and 646 controls aged 7–19 years, found an OR of 1.36 (95% CI: 0.92–2.02) for regular users vs. non-users, but no evidence of a trend in risk with amount of use. Study participants were young (median 13 years old) with limited duration of phone use (median 2.7 years); hence, the study provides insufficient information on a possible association between use of mobile phones in childhood and adolescence and risk of BTs.

To assess the possible association between BT risk and EMF dose from mobile communication technologies in childhood and adolescence, MOBI-Kids, a multinational case-control study of BTs in young people, was conducted in 14 countries: Australia, Austria, Canada, France, Germany, Greece, India, Israel, Italy, Japan, Korea, the Netherlands, New Zealand and Spain, using a common core protocol, with cases recruited over a period of rapidly increasing use of mobile communication devices in young people (2010–2015).

The current paper presents the results of the main MOBI-Kids analyses on risk of brain tumours in young people from use of wireless phones and the ELF and RF dose from them.

2. Methods

Cases were patients aged 10–24 years diagnosed with a benign or malignant BT (see Supplemental Table S1 for list of eligible diagnoses) between 2010 and 2015 in the participating countries. Cases were identified actively in the neurological and neurosurgical facilities in the study regions. All diagnoses were histologically confirmed or based on unequivocal diagnostic imaging. To maximise the statistical power to detect a risk related to RF dose if it exists, tumours originating in the middle of the brain, where little RF energy deposition from wireless phones is expected (Cardis et al., 2008), were excluded. The other exclusion criteria were insufficient knowledge of the language(s) of the country of study and/or a known genetic syndrome related to BTs (e.g. neurofibromatosis).

Because participation was expected to be low in the general population, especially in the study's age range, the study used hospital controls, specifically patients operated for suspected appendicitis in general surgery departments covering the referral area for cases in the participating centres. Controls were individually matched to cases on sex, age (±1 year for cases below 17 years and ± 2 years for cases aged 17 and over), date of interview (±1 year) and region (large geographical areas within countries, e.g. Province in Canada, Autonomous Community in Spain). Two controls per case were recruited. The detailed MOBI-Kids methods are described elsewhere (Sadetzki et al 2014).

All eligible subjects were invited to participate in the study. Subjects who declined to participate were asked to complete a short non-participation questionnaire to assess the possibility of a non-participation selection bias (Turner et al., 2019).

The study was approved by the ethical committees of all participating hospitals. Cases and controls gave consent to be included in the study; in the case of minors, parents consented on their behalf.

2.1. Collection of information

Each participant responded to a face-to-face questionnaire administered by a trained interviewer mainly at the hospital (during hospitalisation or at the time of a check-up) or at home. Only for a small percentage of participants (4% of cases and 6% of controls) was the interview conducted over the phone. The questionnaire collected detailed information on history of use of mobile communication devices (mobile and cordless Digital Enhanced Cordless Telecommunications (DECT) phones) and Wi-Fi, exposure to domestic sources of EMF such as induction cookers and chargers, occupational history with specific questions on exposure to EMF sources, medical radiation exposure history, medical history, residential history, contact with animals and, in a subset of countries, information on sources of drinking water. Interviewers were asked to report the responsiveness of the interviewee at the end of each interview, separately for the mobile phone use section and the other sections of the interview. The interviewer also handed a mobile phone to the subject and asked to act as if s/he had to call, to validate the information on laterality of use reported in the questionnaire.

Parents were asked to complete a questionnaire regarding exposures that might have occurred prior to conception, during pregnancy, and in the first year of life of the participant.

Information regarding tumour characteristics was collected from medical records in a clinical questionnaire. This included information regarding symptoms prior to diagnosis, diagnostic procedures and surgical and pathological information on the tumour (Zumel-Marne et al., 2020).

Tumour location was assessed by one neuroradiologist in each country who reviewed the diagnosing MRI (or CT if MRI was not available) of the cases and marked the location of the tumours on a 3D Grid, using the XGridMaster software developed by Telecom Paris, an adaption of the software used in the INTERPHONE study (E Cardis et al., 2011). This software allows locating the tumour in 1 cm cubic cells in 4 different brain models (children: 8, 11 and 14 years and adult: 34 years), depending on the age of the case (Calderón et al., n.d.). This information was projected onto a reference brain with all brain structures (temporal, frontal, parietal, occipital lobes, cerebellum and structures in the middle brain). We assigned the tumour to the anatomical structure in which the majority of its cells were located for analyses of tumour location.

To validate reported mobile phone use, two validation studies were conducted. The first, including both cases and controls, consisted of obtaining records of mobile phone operator for all consenting subjects and comparing number and duration of calls from these with those reported in the questionnaire. About 25% of subjects agreed to participate in this study (van Wel et al., 2021). In the second study, MOBI-Expo, controls and general population volunteers were asked to install a software application, XMobiSense, developed by Telecom Paris, on their phone to record their phone use over four weeks. The app recorded number and duration of voice calls, number of text messages, amount of data transferred, laterality (percentage of call time the phone was near the right or left side of the head, or neither) and hands-free usage. Participants were asked to report their phone use during this period using a minimally modified version of the MOBI-Kids questionnaire 6 and 18 months after using the application and reported use was compared to the information recorded by the app (Goedhart et al., 2018).

All study centres sent the anonymized electronic questionnaire data to the coordinating centre of the study (ISGlobal, Spain), where they were validated and combined into a central database.

2.2. Exposure assessment

Two complementary main analyses were conducted to assess the association between BT risk and exposures to EMF from mobile communication technologies in young people:

- analyses of BT risk in relation to the history of use of wireless communication devices (mobile and cordless phones); and
- analyses of BT risk in relation to estimates of RF and ELF dose from use of wireless phones (see below).

Regular phone use was defined as having made or received calls at least once a week for a period of 3 months or more. For regular users, the main phone use variables considered were time since start of use (in years), lifetime cumulative number of calls and lifetime cumulative call time (in hours) excluding hands-free use. These variables were calculated separately for mobile and cordless phones. Time since start of use of wireless phones was calculated as the earliest of the dates of start mobile phone use and cordless phone use. The cumulative number of calls (and cumulative call time) with wireless phones was calculated as the sum of the cumulative number of calls (call time) made with mobile phones and those made with cordless phones. To allow for a latency period of one year and prevent a possible reverse causation bias, all variables, except time since first use, were censored at 1 year before the reference date. The date of diagnosis of the case (defined as the date of the first image showing a space-occupying lesion) was used as the reference date for cases and their matched controls.

A common protocol was applied to impute missing data for cases and controls. Briefly, the study questionnaire allowed ranges to be given instead of exact answers to several questions, including number and duration of calls and dates of start and end of wireless phone use. In such instances, analyses were based on the mid-point of the reported range. If data on the age at start or stop of wireless phone or number or duration of calls were missing, these were imputed based on the average of each variable among the participants in the same country, sex and age.

For periods when a subject reported using hands-free devices or the speaker of their mobile or cordless phone, the amount of use was reduced by 18.5%, 7% or 3.5%, depending on whether the devices were used half the time or more, less than half the time, or never or rarely. These values were determined from the results of the MOBI-Expo validation study (Goedhart et al., 2018). Similarly, if hands-free use was through a Bluetooth device, the reduction factors were 10%, 1% and 0% respectively.

Since results of the MOBI-Expo validation study show that laterality was poorly recalled by study participants, analyses of BT risk in relation to mobile phone history did not take reported laterality into account. Laterality was, however, taken into account in the ELF and RF dose estimates; for these, laterality of phone use was attributed as follows, based on the results of the validation study: 70% and 30%, respectively, on the right and left side, for subjects who reported use mainly on the right side of the head; 50% and 50% for those who reported use predominantly on the left; and 60% and 40% for subjects who reported using the phone on both sides of the head.

Analyses in relation to ELF and RF dose from wireless phones were based on the algorithms developed in MOBI-Kids to estimate cumulative and time-weighted average ELF-induced current density (CICD) and cumulative RF specific energy (CSE) absorbed at the centre of gravity (COG) of the tumour of the cases (Calderón et al., n.d.). The algorithms took into account the entire wireless phone history of the subjects, combining the reported information on duration of calls in different time periods with the characteristics of the networks and telephones reported to have been used, as these influence the amount and distribution of ELF and RF dose across the brain. The algorithms also take into account the use of hands-free devices and the reported laterality using the assumptions described above. For these analyses, controls were assigned the tumour location of the case to which they had been matched. These algorithms were applied to estimate ELF CICD and RF CSE from mobile phones and cordless phones separately; the resulting quantities were summed over phone type to obtain the overall ELF CICD and RF CSE.

2.3. Age

The study recruited cases aged 10 to 24 years old, a range in which mobile phone use varies greatly. Most of the youngest subjects had low use of mobile phones, falling mostly in the lowest quintiles of mobile phone use in the study; conversely, most of the older subjects were in the highest quintiles of use. Since age was taken into account in the analyses through the matching, there was little variability of use at any given age. To address this issue, study participants were categorized into three groups 10–14, 15–19 and 20–24 years of age – and age-specific quintiles of use (and of ELF and RF dose) were derived, allowing comparison of risk across quintiles of use within each age category, with possible different susceptibility to RF/ELF-induced BT at different stages of brain development.

As non-regular users (NRUs) represented only 3% and 1% of all participants, respectively, in the 15–19 and 20 + years age groups, they were included in the lowest quintile of use (and of ELF or RF dose) in analyses by level of use or dose. NRUs were grouped together with subjects reporting <1 year of use when analysing time since start.

2.4. Post hoc matching

Though the study protocol required that 2 matched controls be selected for each case, it was not always possible to identify controls fulfilling the matching criteria. To minimize the number of cases without controls, and ensure that matching was as close as possible, *post-hoc* matching was performed, drawing from the pool of all controls recruited for the study. The criteria used for this matching were: same sex and country; age difference at date of diagnosis of the case <1 year for subjects younger than 17 and up to 2 years for those who were older; and difference in interview dates between the case and the control <1 year. The matching on study region required in the original study design was not taken into account as it would have left too many cases without controls and study region was not thought to be related to wireless phone use. The three most closely matched controls were selected for each case (where there were more than 3 eligible controls) and controls could be matched to more than one case (repeat sampling). Ninety nine percent of cases were matched – controls could not be found for only 5 cases.

2.5. Statistical methods

The analyses presented in this paper focus on past wireless (mobile and cordless) phone use as reported by the study participants, as well as on estimated ELF and RF dose as described above. We also analysed other uses of mobile phones at the time of interview: number of text messages sent per day; amount of time (minutes/day) spent sending email, video, files and downloading music and movies; and amount of use of VoIP and of Wi-Fi (minutes/day).

The main analyses were based on conditional logistic regression for matched sets (Breslow and Day, 1987), using the post-hoc matched sets described above to ensure close matching both on age and time period. All analyses were adjusted for parental education (defined as the higher of the mother's and father's achieved education level) and difference between the start date of interviews in the study centre and the date of each participant's interview, within country and region, in categories of 6-month intervals.

Subjects who completed the questionnaire 1 year or more after diagnosis were excluded from the analysis. Furthermore, subjects were excluded if the main section of their questionnaire related to the use of the mobile phone was not completed.

The main analyses focused on NBT, which represented the vast majority (76%) of tumours (Zumel-Marne et al., 2020). Analyses were conducted for NBT as a group, as well as for the glioma subgroup and for high and low grade NBT classified according to the World Health Organization grading (high grade = III and IV; low grade = I and II). Additional analyses are shown of embryonal tumours, the second largest group of cases in the study (14%). It was not possible to analyse other tumour types (meningioma, other non-neuroepithelial) because of the small number of cases in each group. It was decided a priori not to conduct analyses of all BTs as a group due to the high biological diversity of the tumour types in the age-range under study.

Analyses were conducted overall and by age group: 10–14, 15–19 and 20–24 years of age, using age-specific quintiles of the exposure variables. In some analyses by age group, the number of subjects was too small to show all the categories in the time since start variable, so some categories were collapsed. Trends in ORs by level of exposure were tested by fitting the categorical variables as a continuous ordinal variable.

Because absorption of RF energy from mobile phones is highly localized (Cardis et al., 2008; Lee et al., 2019, 2017; Wiart, 2016; Wiart et al., 2008), analyses of wireless phone use variables were also conducted according to the anatomical location of the tumour: temporal lobe, frontal or parietal lobes, cerebellum, and others (occipital and middle brain structures). The main analyses were based on the anatomical location of the majority of tumour cells in the XGridmaster.

For analyses of ELF and RF dose, the main analyses were based on the estimated cumulative induced ELF current density (in μA*hours/m^2) and RF specific energy (in J/kg) at the centre of gravity of the tumour of the cases.

All analyses were carried out for all countries combined and for each country separately.

To account for potential participation bias related to mobile phone use, we conducted an additional analysis of the data using inverse probability of selection weights (Cole and Hernán, 2008), estimated based on the results of the non-participation questionnaire (Turner et al 2019), taking into account mobile phone use, age, sex, maternal education and case-control status. For this, we assumed that all non-participants had the same pattern of phone use as those who responded to the non-participation questionnaire.

No formal analysis was conducted to take into account a possible differential recall bias, since the results of the operators' validation study provided no evidence for differential recall between cases and controls (van Wel et al., 2021).

A series of sensitivity analyses was carried out to evaluate the robustness of the results: use of general quintiles (calculated for participants of all ages together) instead of age-specific quintiles; excluding subjects with imputations; excluding subjects who reported implausible amounts of phone use (more than 50,000 calls or 5,000 h of call over their life), interviewed by less experienced interviewers (with <10 interviews), or interviewed more than 3 and 6 months after diagnosis; adjusting for other uses of phones and communication systems (current use of phone for texting, sending emails and videos and downloading; use of Wi-Fi); use of the original matching of the study; analyses in which each control is matched to only one case to minimise re-use of

Table 1
Main characteristics of the study participants.

	All		Neuroepithelial	
	Cases N (%[1]) = 899	Controls N = 1910	Neuroepithelial N = 671*	Matched Controls N = 1889**†
Sex				
Female	387 (43.0%)	830 (43.5%)	300 (44.7%)	845 (44.7%)
Male	512 (57.0%)	1080 (56.5%)	371 (55.3%)	1044 (55.3%)
Age category				
10–14 years	378 (42.0%)	783 (41.0%)	287 (42.8%)	805 (43.6%)
15–19 years	290 (32.3%)	636 (33.3%)	217 (32.3%)	616 (32.6%)
20–24 years	231 (25.7%)	491 (25.7%)	167 (24.9%)	468 (25.8%)
Country				
Australia	24 (2.7%)	47 (2.5%)	17 (2.5%)	36 (1.9%)
Austria	24 (2.7%)	49 (2.6%)	18 (2.7%)	49 (2.6%)
Canada	23 (2.6%)	24 (1.3%)	18 (2.7%)	27 (1.4%)
France	102 (11.4%)	186 (9.7%)	75 (11.2%)	224 (11.9%)
Germany	84 (9.3%)	135 (7.1%)	68 (10.1%)	200 (10.6%)
Greece	54 (6.0%)	87 (4.5%)	39 (5.8%)	96 (5.1%)
India	24 (2.7%)	37 (1.9%)	16 (2.4%)	30 (1.6%)
Israel	99 (11.0%)	192 (10.1%)	74 (11.0%)	220 (11.7%)
Italy	160 (17.8%)	342 (17.9%)	123 (18.3%)	367 (19.4%)
Japan	30 (3.3%)	224† (11.7%)	24 (3.6%)	72 (3.8%)
Korea	30 (3.3%)	98 (5.1%)	24 (3.6%)	65 (3.4%)
New Zealand	16 (1.8%)	29 (1.5%)	13 (1.9%)	30 (1.6%)
Spain	208 (23.1%)	422 (22.1%)	145 (21.6%)	435 (23.0%)
The Netherlands	21 (2.3%)	38 (2.0%)	17 (2.5%)	38 (2.0%)
Educational level of parents				
High school or less	313 (34.8%)	547 (28.6%)	225 (33.5%)	548 (29.0%)
Medium level tech/prof school	250 (27.8%)	454 (23.8%)	196 (29.2%)	446 (23.6%)
University	219 (24.4%)	538 (28.2%)	162 (24.1%)	498 (26.4%)
Post-graduate university	59 (6.6%)	171 (9.0%)	44 (6.6%)	188 (10.0%)
Other	8 (0.9%)	11 (0.6%)	7 (1.1%)	14 (0.7%)
Don't know	50 (5.6%)	189 (9.9%)	37 (5.5%)	195 (10.3%)
Recall of mobile phone use				
No use of mobile phone	119 (13.2%)	199 (10.4%)	85 (12.7%)	197 (10.4%)
Very well or well	531 (59.1%)	1312 (68.7%)	394 (58.7%)	1275 (67.5%)
Fairly well	159 (17.7%)	280 (14.7%)	124 (18.5%)	291 (15.4%)
Not well or not at all	84 (9.3%)	91 (4.8%)	65 (9.7%)	109 (5.8%)
Don't know	6 (0.7%)	28 (1.5%)	3 (0.4%)	17 (0.9%)
Interviewee				
Index	250 (27.8%)	910 (47.7%)	182 (27.1%)	836 (44.3%)
Parent(s)	135 (15.0%)	124 (6.5%)	96 (14.3%)	132 (7.0%)
Both	503 (56.0%)	845 (44.2%)	384 (57.2%)	899 (47.6%)
Other/don't know	11 (1.2%)	31 (1.6%)	9 (1.4%)	22 (1.2%)
Morphology				
Neuroepithelial tumours				
Glioma	556 (61.8%)	NA	551 (82.1%)	NA
Other neuroepithelial	120 (12.9%)	NA	120 (17.9%)	NA
Non-neuroepithelial tumours				
Embryonal	129 (14.3%)	NA	NA	NA
Meninges	47 (5.23%)	NA	NA	NA
Choroid plexus tumours	15 (1.67%)	NA	NA	NA
Cranial paraspinal nerves	21 (2.34%)	NA	NA	NA
Other	11 (1.22%)	NA	NA	NA

[1]Percentages shown are by column (% by sex, age group, country, etc).
*This includes only neuroepithelial BT cases with at least one matched control (671 of the 676 NBT cases).
** This includes repeated controls: the same control could be matched to more than one case.
†The large number of controls in Japan is due to the selection of large numbers of potential frequency matched controls at the onset of the project.

controls; excluding mobile phone use in the 5 years before diagnosis to rule out a possible prodromal effect, with symptoms of the BT affecting phone use before diagnosis of the cases; by type of respondent (study subject, proxy, both); using strata of sex, age-category and country (with and without stratification on education level) instead of the matched sets in the conditional logistic regression; using unconditional logistic regression; stratified by how well the subjects appeared to recall their mobile phone use according to the interviewers (in two categories: not well/not at all vs. very well/well); by anatomical location based on the topography code of the ICD-O diagnosis; by tumour type; analyses of mobile and cordless phones uses separately; and analyses of the influence of individual countries, sequentially dropping one country at a time.

For analyses of ELF and RF dose, sensitivity analyses were conducted based on the estimated average and maximum induced ELF current density and RF specific energy over the entire tumour of the cases, as well as analyses of ELF and RF dose from mobile and cordless phones separately.

Statistical analysis was conducted using Stata version 14.1 and R version 3.3.

3. Results

The study identified 1,257 eligible cases and 3,539 controls. From those, 899 cases and 1,910 controls participated and completed the interview, mainly at the hospital (56% of cases and 48% of controls) or at home, and mainly after surgery (94% of cases and 98% of controls). The response rate was 72% for cases, ranging from 51 to 96% depending

on the country, and 54% for controls, ranging from 34 to 97% (Supplemental Table S2). Participation was similar in females and males and tended to decrease with increasing age. Participation was lower among those whose mothers had a high school education or less, both among cases (37%) and controls (32%), compared to respondents to the non-participation questionnaire (49% cases; 50% controls) (not shown). The main reason for non-participation in the study was refusal (49% of non-responding cases and 59% of non-responding controls), either by the subject or their parents. Additional reasons for non-participation among non-responding cases were unable to locate (41%), deceased or too ill to be interviewed (4%), medical doctor's refusal (3%) and other reasons (4%). For non-responding controls, apart from direct refusal, 39% could not be located and 2% did not participate for other reasons. Additionally, 3 cases and 12 controls were excluded from the analyses because the questionnaire section regarding wireless phone use was not completed. Among participants who were regular wireless phone users, imputations for missing values had to be made for between 0.3% of subjects for approximate duration of calls (6 cases and 3 controls) and 1.7% for start or stop year related to change of operator (7 cases and 32 controls).

The main characteristics of cases and their controls are presented in Table 1, for all BTs as a group and NBTs specifically. There were slightly more males than females (55 vs 45% among NBT cases) as expected in this age range, and more younger subjects (aged 10–14) than older subjects (15–19 or 20–24), reflecting the higher incidence rates in this age group, as well as different participation rates. Parents of controls had higher educational levels, with 37% reporting university education versus 31% of cases' parents. Ease of recall, as assessed by the interviewer, was better in controls, with over 67% of controls judged to recall their mobile phone history well or very well compared to 59% of cases. Twenty-seven percent of cases vs 44% of controls answered the questionnaire on their own; the identity of the respondent varied by age: 11% of cases and 21% of controls responded themselves in the 10–14 years age group compared to 54% and 83% respectively in the 15–19 and 20–24 years age groups (not shown).

The main analyses included 671 NBT cases and 1,889 controls. Use of wireless phones differed greatly by age (Table 2): among 10–14 years olds, 77% were regular users, compared to 97% and 99%, respectively, in the 15–19 and 20–24 years age groups. Differences were also seen in time since start of use: the median was 5 years before diagnosis among the youngest subjects vs 10 years in the oldest group. Long-term users (10 years or more) represented 22.5% of subjects overall; 7, 21 and 51%, respectively in the 10–14, 15–19 and 20–24 years age groups. Similar differences were seen between age groups in cumulative number of calls and cumulative call time. Median lifetime number of calls reported was 3,156, ranging from 1,075 in the younger age group to 8,427 in the older age group (20–24 years). A similar pattern was seen for total reported duration of calls, with a median of 177 h, ranging from 53 h in the youngest age group to 655 in the oldest. Controls tended to report slightly higher uses of phones than cases.

3.1. Analyses by history of wireless phone use

Results of analyses by history of wireless phone use are shown in Table 3. The OR for NBTs related to having used wireless phones regularly was 0.85 (95% CI 0.62–1.18). ORs were below one in virtually all categories of wireless phone use. A monotonic decreasing trend in ORs was seen with increasing number of years since start of wireless phone use overall, mainly driven by the 15–19 years age group (Table 3 and Supplemental Table S3). Cumulative number of calls was not associated with NBT risk, except in the 15–19 years old group where a trend of decreasing risk with increasing number of calls was seen. ORs were around 0.7 in the three highest quintiles of cumulative call time, and a decreasing trend in ORs was seen overall and in the 15–19 years age group. Results using general quintiles of use (Supplemental Table S4) show a similar decreasing trend overall in ORs as a function of cumulative call time, again based on decreasing trends in the 15–19 years age group for cumulative call time, as well as in the 20–24 years age group. For cumulative number of calls, a decreasing trend was observed only in the 15–19 years age group.

Results were similar in females and males and when mobile phone and cordless phone use were analysed separately (Supplemental Table S3). No single country appeared to unduly influence the results (Fig. 1). Little change in ORs was seen when removing parental education from the model, using the original matching or post-hoc matching with controls matched to one case only (Supplemental Table S5), excluding subjects with imputed phone use (Supplemental Table S6), using unconditional logistic regression or excluding subjects who reported implausible amounts of phone use, subjects interviewed by less experienced interviewers (who conducted <10 interviews) and subjects interviewed more than 3 or 6 months after diagnosis (not shown).

ORs were around 1 when analyses were adjusted for phone data and Wi-Fi use (Supplemental Table S6). Analyses of other uses of phones at the time of interview (not shown) showed a trend in decreasing ORs with increasing use of text messages and increased ORs in the second and third tertiles of VoIP use, based on small number of subjects having reported this use. Use of phones for text messages was strongly correlated with wireless phone history variables (not shown).

Adjusting for a possible participation bias using inverse probability weighting had little impact on the ORs (Supplemental Table 6). Results changed little when restricting analyses to subjects reported by the interviewers to have recalled their mobile phone use history well or very well (Supplemental Table S7). Analyses by respondent type overall (Supplemental Table S8) and by age group (not shown) showed ORs that were consistently below 1 when the respondent was a parent only, with ORs around 1 when the respondent was the index (i.e. the case or control him or herself) or the index with a parent.

Excluding interviews where the respondent was a proxy only (parent

Table 2
Distribution of wireless phone use among NBT cases and controls (combined), overall and by age group.

	OVERALL	10–14 years	15–19 years	20–24 years	Cases	Controls
Regular users* :						
N	2274	840	806	628	590	1684
%	*89%*	*77%*	*97%*	*99%*	*88%*	*89%*
Time since start						
Median (range)	7.5 (1.1–24.7)	5.0 (1.1–14.6)	7.3 (1.2–18.7)	10.2 (1.7–24.7)	7.3 (1.2–24.7)	7.6 (1.1–24.5)
90th percentile	12.3	9.9	12.0	14.3	12.8	12.3
Cumulative number of calls						
Median (range)	3156 (1.5–201968)	1075 (1.5–77416)	3563 (14–70835)	8247 (15–201968)	3026 (4–201968)	3209 (2–168000)
90th percentile	18,961	6812	17,090	31,411	18,242	19,404
Cumulative call time (hours)						
Median (range)	177 (0–33051)	53 (0–10735)	199 (0–13743)	655 (0–33051)	163 (1–21283)	188 (1–33051)
90th percentile	1758	425	1452	3722	1551	1875

* Regular use was defined as having made or received calls at least once a week for a period of 3 months or more.
NBT: neuro-epithelial brain tumours.

Table 3
Risk of NBT in relation to time since start of wireless phone use: overall and by age category. Analyses adjusted for parental education.

	Overall					10–14 years					15–19 years					20–24 years				
	Cases	**Cont.**	**OR**	**95% CI**		**Cases**	**Cont.**	**OR**	**95% CI**		**Cases**	**Cont.**	**OR**	**95% CI**		**Cases**	**Cont.**	**OR**	**95% CI**	
Regular wireless phone user 1 year before diagnosis																				
No	81	205	**1.00**			70	182	**1.00**			9	18	**1.00**			2	5	**1.00**		
Yes	590	1684	**0.85**	0.62	1.18	217	623	**0.87**	0.61	1.25	208	598	**0.62**	0.26	1.45	165	463	**1.06**	0.19	5.83
Time since start of use of wireless phones (years)																				
< 1 year	81	205	**1.00**			70	182	**1.00**			9	18	**1.00**			2	5	**1.00**		
1–4 years	165	450	**0.88**	0.63	1.24	106	318	**0.82**	0.55	1.20	53	120	**0.79**	0.32	1.94	6	12	**1.76**	0.25	12.53
5–9 years	283	800	**0.83**	0.58	1.19	93	243	**0.98**	0.65	1.49	116	344	**0.55**	0.23	1.34	74	213	**0.97**	0.17	5.43
10 + years	142	434	**0.75**	0.50	1.13	18	62	**0.82**	0.43	1.55	39	134	**0.45**	0.18	1.13	85	238	**1.02**	0.18	5.81
Linear trend test	0.17					0.85					0.02					0.85				
Age specific quintiles of cumulative number of calls with wireless phones[1]																				
NRU,1st_Q	204[2]	543	**1.00**			110	307	**1.00**			60	138	**1.00**			34	98	**1.00**		
2nd_Q	141	335	**1.13**	0.85	1.48	51	124	**1.04**	0.68	1.59	48	119	**0.94**	0.57	1.54	42	92	**1.55**	0.87	2.78
3rd_Q	97	338	**0.71**	0.53	0.96	35	125	**0.72**	0.45	1.15	36	120	**0.62**	0.37	1.05	26	93	**0.87**	0.46	1.63
4th_Q	114	335	**0.85**	0.63	1.13	40	124	**0.88**	0.56	1.38	45	119	**0.78**	0.46	1.30	29	92	**0.92**	0.49	1.72
5th_Q	113	338	**0.84**	0.61	1.15	49	125	**1.09**	0.67	1.76	28	120	**0.47**	0.26	0.84	36	93	**1.15**	0.61	2.15
Linear trend test	0.07					0.81					0.01					0.74				
Age specific quintiles of cumulative call time with wireless phones (hours)[3]																				
NRU,1st_Q	226	543	**1.00**			115	307	**1.00**			61	138	**1.00**			50	98	**1.00**		
2nd_Q	127	335	**0.90**	0.68	1.19	52	124	**1.04**	0.68	1.57	45	119	**0.79**	0.48	1.30	30	92	**0.77**	0.43	1.38
3rd_Q	105	338	**0.73**	0.55	0.98	34	125	**0.76**	0.48	1.21	40	120	**0.67**	0.39	1.13	31	93	**0.70**	0.40	1.21
4th_Q	102	335	**0.68**	0.51	0.92	42	124	**0.90**	0.58	1.42	32	119	**0.52**	0.30	0.91	28	92	**0.57**	0.32	1.03
5th_Q	111	338	**0.74**	0.55	0.99	44	125	**0.84**	0.53	1.34	39	120	**0.61**	0.36	1.04	28	93	**0.65**	0.36	1.17
Linear trend test	0.01					0.36					0.03					0.07				

NBT: neuro-epithelial brain tumours; Cont.: controls; Q: quintile; OR: odds ratio; CI: confidence interval.

[1] Age specific quintiles for cumulative number of calls (Q1 to Q5): Age10-14 years: <282; 282-<750; 750-<1620; 1620-<3891; ≥3891. Age 15–19 years: <1103; 1103-<2738; 2738-<5076.8; 5076.8-<10802; ≥10802. Age 20–24: <2959; 2950-<6582; 6582-<11340; 11340-<19876; ≥19876.

[2] Two cases and their two controls excluded as it was not possible to calculate number of calls.

[3] Age specific quintiles for cumulative call time (hours) (Q1 to Q5): Age 10–14 years: <10.5; 10.5-<36, 36-<82; 82-<220.7; ≥220.7. Age 15–19 years: <47.6; 47.6-<142.7; 142.7-<361; 361-<850; ≥850; Age 20–24 years: <216; 216-<492;492-<1022; 1022–2303; ≥2303.

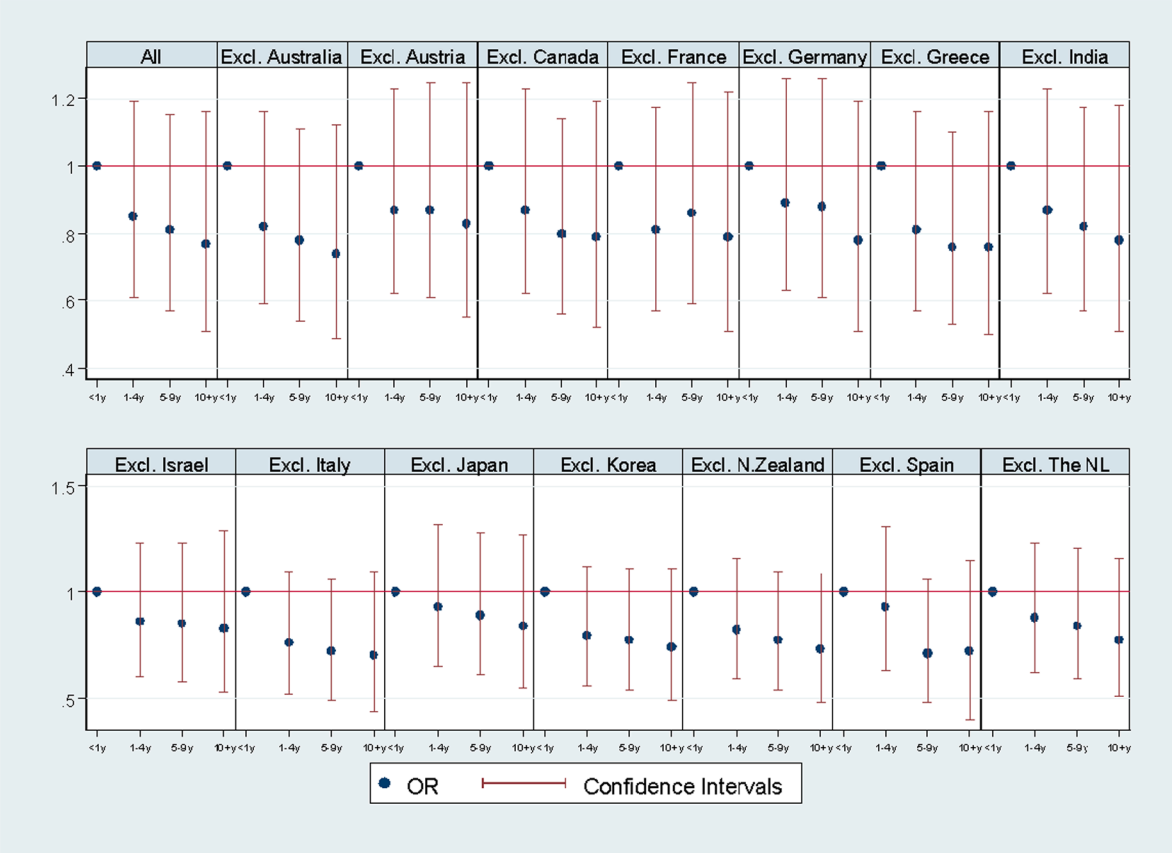

Fig. 1. Risk of NBT in relation to time since first use of wireless phones (in years) – analyses dropping one country at a time. Analyses adjusted for parental education. NBT: neuro-epithelial brain tumours; OR: odds ratio.

Table 4
Risk of NBT related to wireless phone use, overall, using age-specific quintiles – analysis taking into account the main factors influencing the results.

	Excluding proxy interviews					Excluding use in the 5 years before the reference date					Excluding use in the 5 years before the reference date AND proxy interviews				
	Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI	
Time since start of use of wireless phones (years)															
< 1 year	53	133	**1.00**												
1–4 years	130	349	**0.97**	0.64	1.46	246	655	**1.00**			185	553	**1.00**		
5–9 years	248	668	**0.99**	0.65	1.51	283	800	**0.92**	0.72	1.17	249	763	**1.02**	0.78	1.34
10 + years	132	376	**0.96**	0.60	1.54	142	434	**0.82**	0.60	1.13	132	419	**0.99**	0.70	1.40
Linear trend test	0.95					0.23					0.96				
Age specific quintiles of cumulative number of calls with wireless phone															
NRU,1st_Q	152	410	**1.00**			317	903	**1.00**			247	785	**1.00**		
2nd_Q	120	281	**1.23**	0.90	1.67	106	246	**1.21**	0.90	1.61	91	230	**1.25**	0.91	1.70
3rd_Q	83	282	**0.78**	0.56	1.08	73	247	**0.84**	0.61	1.16	66	242	**0.86**	0.61	1.21
4th_Q	106	277	**1.02**	0.74	1.41	77	246	**0.87**	0.63	1.20	72	243	**0.97**	0.69	1.36
5th_Q	101	275	**1.01**	0.71	1.43	98	247	**1.13**	0.83	1.53	90	235	**1.32**	0.94	1.84
Linear trend test	0.69					0.95					0.40				
Age specific quintiles of cumulative call time with wireless phones (hours)															
NRU,1st_Q	174	418	**1.00**			335	903	**1.00**			267	784	**1.00**		
2nd_Q	111	276	**0.97**	0.72	1.32	89	247	**0.96**	0.71	1.30	79	235	**0.97**	0.70	1.33
3rd_Q	91	280	**0.81**	0.59	1.12	76	246	**0.79**	0.58	1.09	66	243	**0.79**	0.56	1.12
4th_Q	88	280	**0.73**	0.53	1.02	78	246	**0.84**	0.61	1.14	71	240	**0.87**	0.62	1.22
5th_Q	99	272	**0.84**	0.61	1.17	93	247	**0.98**	0.72	1.34	83	233	**1.08**	0.77	1.51
Linear trend test	0.10					0.48					0.88				

[1] in analyses excluding use in the 5 years before the reference date, the reference category is NRU and <5 years users.
NBT: neuro-epithelial brain tumours; Cont.: controls; Q: quintile; OR: odds ratio; CI: confidence interval.

or otherwise) gave ORs quite close to 1 for all categories of time since start of use and for cumulative number of calls, as did adjusting for a possible prodromal effect (excluding use in the five years before the reference date). Analyses excluding both proxy only interviews and recent phone use gave ORs distributed around 1 in all categories of the mobile phone use variables (Table 4).

Analyses by tumour location based on the location of the tumours as assessed by neuroradiologists using the XGridmaster are shown in Table 5. There was no apparent association between time since start of use (and systematically reduced ORs for cumulative number of calls and

Table 5
Risk of NBT and time since start of wireless phone use, overall and by age category: analyses by anatomical location of the tumour (adjusted for parental education).

	Temporal					Frontal or Parietal					Cerebellum					Others (including NOS)				
	Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI	
OVERALL																				
Regular wireless phone user 1 year before diagnosis																				
No	12	24	**1.00**			22	62	**1.00**			15	40	**1.00**			28	65	**1.00**		
Yes	59	176	**0.85**	0.33	2.20	226	637	**1.00**	0.55	1.83	83	239	**0.84**	0.40	1.78	181	521	**0.75**	0.43	1.30
Time since start of use of wireless phones (years)																				
< 1 year	12	24	**1.00**			22	62	**1.00**			15	40	**1.00**			28	65	**1.00**		
1–4 years	15	56	**0.70**	0.24	1.98	47	131	**1.04**	0.55	1.96	35	82	**0.97**	0.43	2.17	54	156	**0.74**	0.41	1.33
5–9 years	26	77	**0.91**	0.32	2.57	114	304	**1.00**	0.52	1.94	34	108	**0.72**	0.30	1.71	91	252	**0.79**	0.42	1.46
10 + years	18	43	**1.52**	0.43	5.38	65	202	**0.83**	0.41	1.70	14	49	**0.64**	0.23	1.80	36	113	**0.66**	0.32	1.37
Linear trend test	0.45					0.45					0.31					0.38				
10–14 YEARS																				
Regular wireless phone user 1 year before diagnosis																				
No	7	21	**1.00**			21	50	**1.00**			13	39	**1.00**			27	60	**1.00**		
Yes	25	67	**1.66**	0.43	6.48	54	164	**0.69**	0.35	1.37	48	134	**0.97**	0.44	2.16	79	233	**0.68**	0.38	1.24
Time since start of use of wireless phones (years)																				
< 1 year	7	21	**1.00**			21	50	**1.00**			13	39	**1.00**			27	60	**1.00**		
1–4 years	10	40	**1.12**	0.25	5.04	28	87	**0.63**	0.30	1.33	28	71	**0.98**	0.41	2.32	32	109	**0.59**	0.31	1.14
5 + years	15	27	**2.90**	0.62	13.44	26	77	**0.78**	0.35	1.73	20	63	**0.96**	0.39	2.37	47	124	**0.82**	0.42	1.61
Linear trend test	0.08					0.61					0.94					0.71				
15–19 YEARS																				
Regular wireless phone user 10 years before diagnosis *																				
< 10 years	3	3	**1.00**			1	9	**1.00**			2	1	**1.00**			1	4	**1.00**		
10 + years	20	61	**0.78**	0.10	6.05	83	229	**2.75**	0.33	22.55	18	57	**NA**	NA	NA	68	192	**0.96**	0.10	8.98
20–24 YEARS																				
Regular wireless phone user 10 years before diagnosis *																				
< 10 years	5	24	**1.00**			45	121	**1.00**			10	20	**1.00**			18	48	**1.00**		
10 + years	11	24	**4.16**	0.61	28.24	44	126	**0.93**	0.55	1.57	7	28	**0.79**	0.23	2.72	16	49	**0.51**	0.18	1.44

*For the age groups 15–19 and 20–24 years, we only show results for Regular Phone Users 10 years before diagnosis because for some locations the numbers were too low. For the age group 10–14 years, there were only a few participants in the category 10 + years of use, only the category 5 + years of use is shown.

NBT: neuro-epithelial brain tumours; Cont.: controls; OR: odds ratio; CI: confidence interval; NA: not available – it was not possible to run the analyses due to the low number of cases and controls in this group; NOS: Not otherwise specified.

Table 6
Risk of NBT and time since start of wireless phone use, overall and by age category: analyses by tumour type (adjusted for parental education).

	Neuro-epithelial tumours														Non-neuro-epithelial tumours				
	Glioma					All high-grade					All low-grade					Embryonal tumours				
	Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI	
OVERALL																				
Regular wireless phone user 1 year before diagnosis																				
No	62	150	**1.00**			26	59	**1.00**			55	146	**1.00**			26	55	**1.00**		
Yes	489	1401	**0.83**	0.58	1.20	178	512	**0.74**	0.41	1.33	412	1172	**0.92**	0.62	1.36	103	314	**0.58**	0.31	1.11
Time since start of use of wireless phones (years)																				
< 1 year	62	159	**1.00**			26	59	**1.00**			55	146	**1.00**			26	55	**1.00**		
1–4 years	138	363	**0.89**	0.61	1.31	43	125	**0.81**	0.42	1.53	122	325	**0.94**	0.62	1.42	42	102	**0.83**	0.39	1.73
5–9 years	231	669	**0.78**	0.52	1.17	82	247	**0.66**	0.34	1.25	201	553	**0.95**	0.62	1.46	42	150	**0.50**	0.24	1.05
10 + years	120	360	**0.72**	0.45	1.14	53	140	**0.77**	0.36	1.61	89	294	**0.74**	0.45	1.21	19	62	**0.50**	0.20	1.23
Linear trend test	0.13					0.47					0.23					0.05				
10–14 YEARS																				
Regular wireless phone user 1 year before diagnosis																				
No	56	141	**1.00**			24	51	**1.00**			46	131	**1.00**			21	49	**1.00**		
Yes	177	513	**0.78**	0.52	1.16	52	161	**0.58**	0.29	1.16	165	4642	**1.02**	0.66	1.57	51	155	**0.67**	0.32	1.39
Time since start of use of wireless phones (years)																				
< 1 year	56	141	**1.00**			24	51	**1.00**			46	131	**1.00**			21	49	**1.00**		
1–4 years	87	264	**0.73**	0.48	1.13	22	80	**0.55**	0.25	1.18	84	238	**0.95**	0.60	1.52	31	72	**1.10**	0.45	2.70
5–9 years	75	199	**0.86**	0.54	1.37	23	67	**0.58**	0.26	1.33	70	176	**1.24**	0.75	2.05	17	71	**0.53**	0.21	1.38
10 + years	15	50	**0.74**	0.36	1.50	7	14	**0.89**	0.28	2.83	11	48	**0.72**	0.33	1.60	3	12	**0.46**	0.09	2.41
Linear trend test	0.56					0.49					0.84					0.13				
15–19 YEARS																				
Regular wireless phone user 1 year before diagnosis																				
No	5	13	**1.00**			2	6	**1.00**			7	12	**1.00**			4	5	**1.00**		
Yes	166	470	**0.78**	0.26	2.34	59	166	**1.09**	0.21	5.62	149	432	**0.55**	0.20	1.54	36	110	**0.29**	0.05	1.69
Time since start of use of wireless phones (years)																				
< 1 year	5	13	**1.00**			2	6	**1.00**			7	12	**1.00**			4	5	**1.00**		
1–4 years	45	87	**1.12**	0.36	3.54	18	36	**1.60**	0.28	9.23	35	84	**0.67**	0.23	1.94	10	28	**0.33**	0.04	2.91
5–9 years	92	281	**0.64**	0.20	2.00	33	101	**0.98**	0.18	5.25	83	243	**0.50**	0.17	1.47	16	58	**0.20**	0.02	1.61
10 + years	29	102	**0.49**	0.15	1.63	8	29	**0.70**	0.11	4.56	31	105	**0.42**	0.14	1.26	10	24	**0.39**	0.05	3.28
Linear trend test	0.01					0.22					0.07					0.58				
20–24 YEARS																				
Regular wireless phone user 10 years before diagnosis *																				
< 10 years	71	206	**1.00**			29	90	**1.00**			53	140	**1.00**			11	24	**1.00**		
10 + years	76	208	**1.09**	0.71	1.68	38	97	**1.32**	0.67	2.58	47	141	**0.86**	0.52	1.42	6	26	**0.37**	0.09	1.48

*For the age groups 20–24 years, we only show results for Regular Phone Users 10 years before diagnosis because numbers of subjects were too low in the other time categories.
NBT: neuro-epithelial brain tumours; Cont.: controls; OR: odds ratio; CI: confidence interval

cumulative call time – not shown) and risk of temporal lobe tumours overall, though ORs appeared to increase with increasing time since start of use in the 10–14 years age group and an increased OR was seen for use 10 years or more in the past in the 20–24 years age group, but not in the 15–19 years age group. ORs in the temporal lobe were below 1 in virtually all categories of cumulative number of calls and cumulative call time, with no clear trend by level of dose overall (not shown). Monotonically decreasing trends with increasing time since start were seen for tumours in the cerebellum, in the frontal or parietal lobes and in other parts of the brain; only in the frontal/parietal lobe in the 15–19 years age group was an increased OR seen for use 10 years or more in the past, but the confidence intervals are very wide. Results of analyses of tumour location based on the topography code of the ICD-O diagnosis registered in the clinical records showed similar results (Supplemental Table S9).

We observed similar associations when analysis was limited to gliomas or when stratified to high-grade and low-grade tumours (Table 6). Odds ratios were more variable in the age-specific analyses.

Table 6 also shows the results of analyses of embryonal tumours, the second most frequent type of BTs in this study. Regular wireless phone use was associated with a reduced OR for embryonal tumours (OR 0.58, 95% CI 0.31–1.11) overall, and in all time since start of use categories. Results by age group were similar, based on very small numbers of subjects.

3.2. Analyses by ELF and RF dose level

ELF and RF dose estimates could be derived for 604 out of 671 NBT cases for whom diagnosing MRIs could be obtained and reviewed by neuroradiologists to identify the location of the tumour on the XGridmaster, as well as for their 1701 controls. The characteristics of these subjects were very similar to those of all NBT cases included in the analyses of wireless phone history (Supplemental Table S10).

Table 7 shows the results of analyses of risk by age-specific quintile of cumulative RF specific energy (CSE) and ELF induced current density (CICD) at the centre of gravity of the tumour and, as a sensitivity analysis, in the XGridmaster cell of the tumour with the highest RF CSE and ELF CICD respectively. A monotonically decreasing trend in risk was observed overall for RF (Table 7), as well as in the 15–19 years old age group. For ELF, a decreasing trend was also seen overall and in the 15–19 years old age group, with reduced ORs at all levels of ELF CICD in the 20–24 years old age group (Table 7). Analyses of RF CSE and ELF CICD from mobile and cordless phones separately (Supplemental Table S11) showed similar patterns of ORs. Analyses by ELF time-weighted average CICD showed similar results to the cumulative CICD analysis (not shown).

Adjusting for a possible participation bias using inverse probability weighting had little impact on the ORs (not shown). Adjusting for recall by excluding interviews where the respondent was a proxy only (parent or otherwise) gave ORs quite close to 1 for all categories of RF and ELF dose (Table 8), as did adjusting for a possible prodromal effect. Excluding both proxy only interviews and recent use gave ORs distributed around 1 in all categories of RF CSE and ELF CICD (Table 8).

Analyses by tumour type are shown in Supplemental Table S12. ORs for glioma, and high- and low-grade NBT were mostly below one, with no clear overall trend. For embryonal tumours, reduced ORs were seen in the highest quintiles of RF CSE and ELF CICD.

Analyses restricted to subjects judged by the interviewer to recall their phone use well or very well showed a decreasing trend for RF CSE and reduced ORs in all categories of ELF CICD (Supplemental Table S13), while analyses using different analytical strategies (original matching, post-hoc matching with each control being matched to one case only, unconditional logistic regression, stratifying on age-category, sex and country rather than using the matched set in conditional logistic regression) and analyses excluding subjects with implausible levels of use, subjects interviewed by less experienced interviewers and subjects interviewed more than 3 and 6 months after diagnosis had little impact on the risk estimates (not shown).

Though laterality of use was not used in the analyses of wireless phone history – and reliance on laterality was limited in the development of the RF and ELF algorithms (see Methods section for laterality assignment), it is noteworthy that agreement between reported laterality of use and laterality as observed by the interviewer is very good – 98 and 99% respectively for cases and controls who reported use of the phone on the right side of the head; 74 and 88%, respectively for use on the left side of the head when the subject started using mobile phones – and 86 and 92% for current use of the left side of the head (not shown). Only a small proportion of subjects (3% of cases and 2% of controls) reported changes in laterality of phone use.

4. Discussion

The overall pattern of ORs in this study suggest no increased risk of NBT in relation to either use of wireless devices (or mobile or cordless phones separately) or RF CSE or ELF CICD. Increasing time since start of use, cumulative number of calls and cumulative call time were associated with decreased ORs for NBT, results that appear to be driven in particular by observations in the 15–19 year-old age group and proxy interviews. Only in the youngest age-group was there a suggestion of a possible increased risk in relation to time since start of use for tumours in the temporal lobe, based on small numbers of cases.

To our knowledge, MOBI-Kids is the largest case-control study to date of the relation between use of wireless phones (including both mobile and cordless phones) and risk of BTs in children, adolescents and young adults. Compared to previously reported studies, MOBI-Kids included a higher proportion of long-term and heavy users of mobile phones and of wireless phones in general. The vast majority of study participants were regular users of wireless phones, even in the youngest age category and the study included substantially higher numbers of subjects who used phones for 10 years or more than previous studies: 22.5% overall compared to 13.6% among adults in the INTERPHONE study (conducted between 2000 and 2004), the case-control study with the largest number of long-term and heavy users to date. The median reported cumulative call time in MOBI-Kids was 177 h overall, ranging from 53 h in the 10–14 years old to 655 h in the 20–24 years age group, compared to 75 h in the adults in the INTERPHONE study. Overall, 12% of regular phone users in MOBI-Kids reported a cumulative call time of 1,640 h or more (1.3, 9.2 and 36.2% of users, respectively, in the three age-groups), the cut point for the highest decile of use in the INTERPHONE study.

An important strength of MOBI-Kids is the fact that the risk of BTs was analysed in relation to the estimated RF CSE and ELF CICD at the location of the tumour as well as to the amount of wireless phone use. This is particularly important because RF and ELF doses at the tumour site depend not only on the duration and amount of phone use but also on the location of the tumour, the frequency band in which the telephones emit and the emission technology (with much reduced output power in 3G compared to 2G and 1G). Indeed, the agreement between RF and ELF dose estimates and wireless phone use variables is moderate to poor (weighted kappa 0.55 and 0.67 for RF and ELF respectively when compared to cumulative call time overall; weighted kappa close to 0 for 3G mobile phone use only (Calderón et al.)). The absence of a positive association between NBT risk and levels of RF CSE and ELF CICD strengthens our finding of no apparent increased risk of NBT with use of wireless phones (both mobile and cordless). Both mobile phone history and estimates of ELF and RF doses share a number of uncertainties, however, related to the subjects' reporting of their phone use. Our estimates of ELF and RF dose are also subject to additional uncertainty, in particular related to the actual communication systems used during subjects' mobile phone histories.

Age was a major determinant of phone use in this study. To ensure sufficient variability of exposure within age groups, analyses had to be

Table 7
Risk of NBT related to cumulative RF specific energy (CSE) and ELF induced current density (CICD) at the centre of gravity (COG) of the tumour, overall and by age group, using age-specific quintiles – adjusted for parental education.

	Overall					10–14 years					15–19 years					20–24 years				
	Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI	
RF Age specific quintile of cumulative Specific Energy at COG																				
NRU,1st_Q	193	491	**1.00**			113	280	**1.00**			45	121	**1.00**			35	90	**1.00**		
2nd_Q	109	301	**0.92**	0.69	1.23	32	114	**0.68**	0.42	1.11	39	103	**1.18**	0.69	2.03	38	84	**1.10**	0.63	1.93
3rd_Q	111	304	**0.89**	0.65	1.22	34	115	**0.64**	0.39	1.06	44	104	**1.21**	0.69	2.15	33	85	**0.92**	0.49	1.72
4th_Q	90	301	**0.77**	0.55	1.06	40	114	**0.87**	0.54	1.40	32	103	**0.92**	0.50	1.71	18	84	**0.54**	0.27	1.09
5th_Q	101	304	**0.78**	0.56	1.09	44	115	**0.88**	0.54	1.45	29	104	**0.72**	0.38	1.38	28	85	**0.71**	0.36	1.41
Linear trend test	0.09					0.55					0.23					0.11				
ELF Age specific quintile of cumulative Induced Current Density at COG																				
NRU,1st_Q	213	491	**1.00**			111	280	**1.00**			50	121	**1.00**			52	90	**1.00**		
2nd_Q	109	301	**0.81**	0.60	1.08	45	114	**0.95**	0.62	1.47	42	103	**1.05**	0.61	1.78	22	84	**0.44**	0.24	0.81
3rd_Q	80	304	**0.58**	0.42	0.80	24	115	**0.51**	0.30	0.87	33	104	**0.78**	0.43	1.41	23	85	**0.50**	0.28	0.92
4th_Q	90	301	**0.62**	0.45	0.86	33	114	**0.69**	0.41	1.14	32	103	**0.71**	0.39	1.29	25	84	**0.44**	0.23	0.82
5th_Q	112	304	**0.79**	0.58	1.08	50	115	**1.01**	0.63	1.64	32	104	**0.73**	0.40	1.32	30	85	**0.57**	0.31	1.03
Linear trend test	0.03					0.42					0.15					0.06				
RF Age specific quintiles of maximum cumulative Specific Energy in the tumour																				
NRU,1st_Q	195	491	**1.00**			109	280	**1.00**			52	121	**1.00**			34	90	**1.00**		
2nd_Q	115	301	**0.99**	0.74	1.33	31	114	**0.68**	0.41	1.13	39	103	**0.96**	0.57	1.62	45	84	**1.47**	0.84	2.56
3rd_Q	93	304	**0.72**	0.52	1.00	34	115	**0.71**	0.43	1.17	32	104	**0.66**	0.36	1.20	27	85	**0.85**	0.44	1.61
4th_Q	101	301	**0.82**	0.60	1.13	47	114	**1.06**	0.66	1.70	34	103	**0.76**	0.42	1.34	20	84	**0.58**	0.29	1.16
5th_Q	100	304	**0.76**	0.54	1.07	42	115	**0.90**	0.54	1.49	32	104	**0.63**	0.34	1.18	26	85	**0.70**	0.35	1.41
Linear trend test	0.07					0.90					0.14					0.04				
ELF Age specific quintile of maximum cumulative Induced Current Density in the tumour																				
NRU,1st_Q	210	491	**1.00**			108	280	**1.00**			48	121	**1.00**			54	90	**1.00**		
2nd_Q	103	301	**0.81**	0.60	1.09	39	114	**0.86**	0.54	1.36	42	103	**1.20**	0.70	2.04	22	84	**0.43**	0.23	0.80
3rd_Q	89	304	**0.67**	0.49	0.91	29	115	**0.68**	0.41	1.12	36	104	**0.87**	0.48	1.59	24	85	**0.47**	0.26	0.85
4th_Q	89	301	**0.64**	0.46	0.88	35	114	**0.79**	0.49	1.29	30	103	**0.72**	0.39	1.32	24	84	**0.38**	0.20	0.73
5th_Q	113	304	**0.84**	0.61	1.15	52	115	**1.15**	0.72	1.85	33	104	**0.80**	0.44	1.45	28	85	**0.51**	0.28	0.94
Linear trend test	0.09					1.00					0.18					0.03				

**Age-specific quintiles for RF CSE at COG (Q1 to Q5): Age 10–14: <4.6e-04/4.6e-04 to < 2.06e-03/2.06e-03 to < 7.1e-03/7.1e-03 to < 3.4e-02/≥3.4e-02. Age 15–19: <6.67e-03/6.67e-03 to < 2.9e-02/2.9e-02 to < 9.4e-02/ 9.4e-02 to < 3.3e-01/ ≥3.3e-01. Age 20–24: <5.07e-02/ 5.07e-02 to 1.6e-01/1.6e-01 to < 4.38e-01/4.38e-01 to < 1.119/ ≥1.119 J/kg.
Age-specific quintiles for ELF CICD at COG (Q1 to Q5): Age 10–14: <1.88e-06/ 1.88e-06 to < 6.43e-06/ 6.43e-06 to < 1.473e-05/ 1.473e-05 to < 5.0e-05/ ≥5.0e-05. Age 15–19: <1.48e-05/ 1.48e-05 to 5.63e-05/ 5.63e-05 to < 1.58e-04/ 1.58e-04 to < 4.11e-04/ ≥4.11e-04. Age 20–24: <1.35e-04/ 1.35e-04 to < 3.12e-04/ 3.12e-04 to < 6.68e-04/ 6.68e-04 to < 1.68e-03/ ≥1.68e-03 μA*hours/m^2.
Age-specific quintiles for maximum RF CSE in the tumour (Q1 to Q5): Age 10–14: <1.012e-03/1.012e-03 to < 4.8e-03/4.85e-03 to < 1.5395e-02/1.5395e-02 to < 7.58e-02/≥7.58e-02. Age 15–19: <1.34e-02/ 1.34e-02 to < 5.97e-02/ 5.97e-02 to < 1.9e-01/ 1.9e-01 to < 7.1e-01/ ≥7.1e-01. Age 20–24: <0.1258/ 0.1258 to < 0.38/ 0.38 to < 1.04/ 1.04 to < 2.88/≥2.88 J/kg.
Age-specific quintiles for maximum ELF CICD in the tumour (Q1 to Q5): Age 10–14: <3.006e-06/ 3.006e-06 to < 9.95e-06/ 9.95e-06 to < 2.499e-05/ 2.499e-05 to < 8.34e-05/ ≥8.34e-05. Age 15–19: <2.02e-05/ 2.02e-05 to < 8.6e-05/ 8.6e-05 to < 2.2247e-04/ 2.2247e-04 to < 6.0e-04/ ≥6.0e-04. Age 20–24: <2.18e-04/ 2.18e-04 to < 5.19e-04/ 5.19e-04 to < 9.9e-03/ 9.9e-03 to < 2.64e-03/ ≥2.64e-03 μA*hours/m^2.
NBT: neuro-epithelial brain tumours; Cont.: controls; Q: quintile; OR: odds ratio; CI: confidence interval; ELF: extremely low frequency electromagnetic fields; RF: radiofrequency electromagnetic fields.

Table 8
Risk of NBT related to cumulative RF specific energy (CSE) and ELF induced current density (CICD) at the centre of gravity (COG) of the tumour, overall and by age group, using age-specific quintiles – analysis taking into account the main factors influencing the results.

	Excluding Proxy interviews					Excluding use in the 5 years before the reference date					Excluding use in the 5 years before the reference date AND proxy interviews				
	Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI		Cases	Cont.	OR	95% CI	
RF Age specific quintile of cumulative Specific Energy at COG															
NRU,1st_Q	146	374	**1.00**			299	815	**1.00**			232	705	**1.00**		
2nd_Q	99	250	**1.03**	0.74	143	78	220	**0.96**	0.70	1.33	72	216	**1.07**	0.76	1.51
3rd_Q	96	251	**1.01**	0.71	1.44	69	223	**0.88**	0.63	1.22	67	215	**1.01**	0.71	1.44
4th_Q	77	247	**0.89**	0.62	1.29	73	220	**0.89**	0.64	1.24	57	212	**0.83**	0.57	1.20
5th_Q	88	252	**0.86**	0.59	1.26	85	223	**1.03**	0.74	1.44	80	213	**1.20**	0.83	1.73
Linear trend test	0.35					0.83					0.79				
ELF Age specific quintile of cumulative Induced Current Density at COG															
NRU,1st_Q	165	376	**1.00**			297	815	**1.00**			235	707	**1.00**		
2nd_Q	96	247	**0.84**	0.61	1.16	79	220	**1.03**	0.76	1.41	68	214	**1.01**	0.72	1.41
3rd_Q	70	257	**0.62**	0.44	0.89	62	223	**0.74**	0.52	1.04	58	215	**0.82**	0.57	1.18
4th_Q	76	247	**0.66**	0.46	0.95	78	220	**0.98**	0.71	1.37	69	214	**1.01**	0.71	1.44
5th_Q	99	247	**0.87**	0.61	1.23	88	223	**1.10**	0.80	1.51	78	211	**1.18**	0.83	1.69
Linear trend test	0.19					0.85					0.55				

NBT: neuro-epithelial brain tumours; Cont.: controls; Q: quintile; OR: odds ratio; CI: confidence interval; ELF: extremely low frequency electromagnetic fields; RF: radiofrequency electromagnetic fields.

conducted based on age-specific quintiles of use and of RF and ELF dose, as older subjects tended to cluster in the higher quintiles of these variables and younger subjects in the lower quintiles when analyses used quintiles based on the overall distribution of these variables. This limited the statistical power of the study by reducing the exposure contrast in individual age groups.

We carried out a large number of sensitivity analyses. Results were similar in females and males, were not influenced by parental education, were generally not sensitive to analytical strategy and no individual country appeared to influence the observed trend of decreasing risk with increasing use. Restricting analyses to subjects who were judged by the interviewer to recall their mobile phone use well or very well had little impact on these results. Excluding proxy interview and the most recent 5 years of use (to rule out a possible prodromal effect), adjusting for other uses of phones and Wi-Fi all resulted in ORs that were closer to the null, however.

These observations suggest that different sources of bias may play a role in the decreasing trend in ORs observed in relation to both wireless phone use variables and RF and ELF dose. We have no reason to suspect, a priori, that wireless phone use (or the resulting EMF dose to the brain) would reduce BT risk.

The decreasing trend was mainly seen in the 15–19 years old age group. This age-group is characterised by a mixed profile of respondents, with substantially more cases than controls with proxy only respondents. While among the 10–14 years old, most of the interviews were with a parent and in the 20–24 year old group the subjects tended to respond themselves, in the 15–19 years age group, 41% of subjects responded by themselves and 52% together with a parent. Analyses restricted to interviews with the subject him/herself alone or with a parent gave ORs that were generally closer to 1, suggesting that information on wireless phone history collected from parents (who may be unaware of their children's true) alone may not be reliable. These observations suggest that at least part of the reduced ORs may be related to proxy interviews bias.

Regarding confounding, the analyses presented were adjusted by educational achievement level of parents and difference of time of interviews between cases and controls within countries. The post-hoc matching ensured that cases and their controls were as close as possible with respect to age and interview dates and were of the same sex and country. While the MOBI-Kids study collected information on numerous other potential risk factors for BTs in young people, none of these, a priori, is thought to be a possible confounder of the association between phone use history or RF or ELF dose and NBT risk. Our attempt to adjust for a possible prodromal effect did result in ORs that were closer to 1, so this is also a possible partial explanation for the trends observed.

Risk factors for BTs in young people are largely unknown, however, and we cannot rule out the possibility that residual confounding bias has contributed to our results.

The case-control design of this study makes it prone to a range of biases, which we addressed through a number of sub-studies. Analysis of the non-participation questionnaire data suggested that both prevalence of mobile phone use and percentage of subjects who used phones for 5 years or more tended to be higher among participants than among those who declined to participate (Turner et al., 2019) but our analyses suggest this contributed little to the observed reduced ORs.

Validation of reported mobile phone use of case and controls through review of operator records provided no evidence of a differential recall error between cases and controls (van Wel et al., 2021), hence we did not adjust our analyses for such error. However, the study did indicate both systematic and random non-differential recall errors, with subjects tending to underestimate number of calls and overestimate call duration, with a trend by the level of self-reported mobile phone use: underestimation at lower levels and overestimation at higher levels for both number and duration of calls. As the analyses presented in this paper are based on categorical analyses of wireless phone use and RF and ELF dose, any such under- or over-estimation is not expected to affect our results (only the cut-points of the quintiles would be changed). The observed non-differential recall error may also bias risk estimates, though the direction of any bias is uncertain (Dosemeci et al., 1990), and we have little reason to think it would be likely to explain the decreasing trends observed mainly in the 15–19 years age group.

The factors mentioned above – possibly differential recall in proxies, prodromal effects and non-participation selection bias – are likely to be responsible for at least part of the decreasing trend in ORs observed in this study and, taken together, might explain our findings (Table 4). Despite our best efforts, some unknown bias might also explain our findings. The effect of unknown bias cannot be calculated; therefore we cannot rule out a bias that could have caused the reduced ORs observed in this study, or that could even obscure a real increase in risk of BTs in relation to wireless phone use and ELF and/or RF dose. Indeed, as pointed out by Saracci and Pearce, in the absence of data to evaluate the likely magnitude of the effect of such bias, a weakly elevated risk can actually be concealed under consistently reduced risks (Saracci and Pearce, 2008). Thus we can only discard a strong positive association between wireless phone use and risk of BTs in this study.

The lack of an increased risk in our study are consistent with those of the CEFALO study of BTs in children and adolescents (Aydin et al., 2011)

which included a smaller number of cases, diagnosed between 2004 and 2008, with substantially less phone use. They are also consistent with the overall INTERPHONE study results which found no overall increase in risk in relation to the level of mobile phone use. Unlike INTERPHONE, we found no increased risk in the highest dose group and no RF dose-related increased risk in the longest-term users. Unlike Hardell, we also found no association with amount and number of years of use (Hardell and Carlberg, 2015b). These differences might reflect differences in phone technologies over time, with most phone use among participants of these studies using the 1st and 2nd generations of mobile telephony, compared to the 2nd and 3rd among MOBI-Kids participants (2G, 3G). While differences in output power between these systems were taken into account in the algorithm that estimated the subjects' RF dose in both studies, direct comparison of results of analyses of RF dose between these two studies is not possible, as the algorithm used in MOBI-Kids was improved to factor in advances in dosimetry, such as, among others, the inclusion of heterogenous phantoms, which provide RF dose at the tissue level, as opposed to the homogenous phantom used in INTERPHONE.

Currently, there is no conclusive biological evidence that RF or ELF at the levels emitted by mobile phones may increase the risk of brain cancer (ICNIRP, 2020; SCENIHR, 2015), hence our results are consistent with the knowledge to date. Recent reviews, however, report RF related increased oxidative stress in the majority of animal and cell studies, including experiments made with a variety of cell types, exposure times and SAR levels (Schuermann and Mevissen, 2021). A large number of studies also report potential effects of RF exposure on genotoxicity and gene expression (Lai, 2021). Further, two large long-term careful animal experiments have been conducted to evaluate the potential carcinogenic effects of RF exposure. Both the US National Toxicology Programme (NTP) study and the Italian Ramazzini Institute (RI) study report an increased risk of heart schwannomas (in males only in the NTP study) and of glial cell tumours – in male rats in the NTP study and in females and not statistically significant in the RI study – at the highest dose levels (Falcioni et al., 2018; NTP, 2018; Wyde et al., 2018). Further research is underway to understand these results and the potential biological mechanisms of RF, including a systematic review organised by the World Health Organisation. One possible mechanism by which RF or ELF might affect the risk of cancer is through tumour promotion, thus possibly accelerating the appearance of a tumour which would otherwise have occurred later. Such an effect would translate into a shift in the age-distribution curves of BT incidence (Kundi, 2010). No such shift has been reported to date, though BTs in young people are rare, and the power to observe such a shift is probably low.

Case control studies are not well suited to identify tumour promotion effects (Kundi, 2010). Our results, however, do not exclude a possible brain tumour growth acceleration effect of wireless phone use. It is thought that many tumours of childhood and adolescence may be initiated prenatally or shortly after birth. Tumours eligible for the MOBI-kids study mainly peak therefore in the 3rd year of life and decline afterwards. Hence, in the 10 to 24 years age range, many patients with tumours may have already had a growing mass of neoplastic cells leading to their diagnosed BT after they started wireless phone use. Under these circumstances, wireless phone use could have increased the growth rate of these nascent tumours and led to earlier diagnosis. If then the incidence decreases with age, which is the case in this age range, then the incidence in wireless phone users could fall below the incidence in non-users. As a consequence, the ORs, which are valid estimates of the incidence ratios, could fall below 1 in the face of a tumour promoting effect of wireless phone use.

Although this is the largest study of BTs in young people to date, the numbers of subjects in subgroups are often too small to evaluate possible associations, for example, in specific windows of time, in specific age groups, and in different anatomical locations of tumours. There are also too few cases to study effects on any BT type except NBTs, which, though more homogeneous than other BT types, are not a completely homogeneous group of tumours and may have different risk factors (including, possibly, EMF from wireless phones) for different histologic subtypes. BTs in young people are rare, however, and even with a median of 3 years of case recruitment in most participating centres, the present 14-country study could only recruit 899 BT cases, of which 671 were NBT.

5. Conclusions

In this large multi-national case-control study of BTs, no increased risk of neuroepithelial BTs was observed either in relation to wireless phone use or to estimated ELF or RF dose from wireless phones. Decreasing trends in risk in relation to time since start of use and cumulative call time were observed. We have no a priori reason from research in humans to believe that this reflects a protective effect of wireless phone use in humans. Analyses suggest that this finding, mainly attributable to observations in the 15–19 years old age group, could be explained by differential recall in proxies and prodromal effects. Moreover, we cannot rule out residual confounding from sources we have not identified, despite our best efforts in identifying possible confounders. Therefore, while our study provides no evidence of a causal association between wireless phone use and BTs in young people, possible sources of residual bias prevent us from ruling out a small increase in risk due to this use.

Declaration of Competing Interest

M Kundi is an expert witness in a court case in Washington D.C.

Although not a competing financial interest, D. Krewski holds a peer-reviewed university-industry chair in risk science administered by the Natural Sciences and Engineering Research Council of Canada (NSERC – Industrial Research Chairs Grants (nserc-crsng.gc.ca)). The Canadian Wireless Telecommunications Association was a past partner in this program, but had no active role in the research program of the Chair, which operates independently of the industrial partners. Dr. Krewski also serves as Chief Risk Scientist and CEO for Risk Sciences International (www.risksciences.com) a Canadian company established in 2006 in partnership with the University of Ottawa, which has conducted contract work on radiofrequency fields for Canadian federal government clients. F. Momoli also is a scientist at Risk Sciences International.

Before 2015 J Wiart was an employee of Orange. At that time, his work in the study was limited to dosimetry. In 2015 he became Ingenieur General des Mines, employed by the Institut Mines-Télécom, a state academic institute. J Wiart has no conflict of interest to declare.

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