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A population-based case–control study of radiofrequency exposure in relation to childhood neoplasm

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HIGHLIGHTS

- We investigated neoplasm risk of children with potentially elevated exposure to RF.
- RF exposure was indicated by power density associated with mobile phone base stations
- Higher-than-median RF exposure level significantly increases the risk for all neoplasm combined.
- Higher RF doesn't significantly increase the risk of leukemia or brain neoplasm.

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ABSTRACT

This population-based case–control study in Taiwan considered incident cases aged 15 years or less and admitted in 2003 to 2007 for all neoplasm (ICD-9-CM: 140–239) ($n=2606$), including 939 leukemia and 394 brain neoplasm cases. Controls were randomly selected, with a case/control ratio of 1:30 and matched on year of birth, from all non-neoplasm children insured in the same year when the index case was admitted. Annual summarized power (ASP, watt-year) was calculated for each of the 71,185 mobile phone base stations (MPBS) in service between 1998 and 2007. Then, the annual power density (APD, watt-year/km^2) of each township ($n=367$) was computed as a ratio of the total ASP of all MPBS in a township to the area of that particular township. Exposure of each study subject to radio frequency (RF) was indicated by the averaged APD within 5 years prior to the neoplasm diagnosis (cases) or July 1st of the year when the index case was admitted (controls) in the township where the subject lived. Unconditional logistic regression model with generalized estimation equation was employed to calculate the covariate-adjusted odds ratio [AOR] of childhood neoplasm in relation to RF exposure. A higher than median averaged APD (approximately 168 WYs/km^2) was significantly associated with an increased AOR for all neoplasms (1.13; 1.01 to 1.28), but not for leukemia (1.23; 0.99 to 1.52) or brain neoplasm (1.14, 0.83 to 1.55). This study noted a significantly increased risk of all neoplasms in children with higher-than-median RF exposure to MPBS. The slightly elevated risk was seen for leukemia and brain neoplasm, but was not statistically significant. These results may occur due to several methodological limitations.

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1. Introduction

Mobile (cellular) phones, mostly operated at radiofrequency (RF) frequencies of 800 MHz to 900 MHz and 1800 MHz to 2200 MHz, have been in use since the early 1980s. A number of studies on their potential health effects have been extensively conducted since then. Primary concern has been related to the risk of neoplasm in the exposed intracranial tissues in the proximity of the mobile phone (Auvinen et al., 2006; INTERPHONE Study Group, 2010; Repacholi et al., 2012). Generally, there is no support for a causal relationship between the use of wireless phone and the incidence of adult cancers in areas in the head, but data are insufficient to make any determination about longer-term use (i.e., >10 years) (Repacholi et al., 2012). In response to an increased utilization of mobile phones, installation and operation of mobile phone base stations (MPBS) have grown over the past decade, resulting in RF exposure almost unequivocally everywhere. MPBS usually emit RF in far-field conditions, i.e., radiation from a source located at a distance of more than one wavelength. These far-field conditions may result in relatively homogeneous whole-body exposure (Röösli et al., 2010).

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Moreover, the MPBS-emitted RF can occur continuously despite the considerably lower levels than the local maximum levels that occur when someone uses a mobile phone handset (Neubauer et al., 2007; Frei et al., 2009). Therefore, the MPBS-emitted RF might pose biological effects different from certain local intracranial effects potentially caused by mobile phone use.

Kim and Park (2010) conducted a measurement study of MPBS-emitted RF at 50 locations in Korea. These locations were within a range of approximately 32 m to 422 m away from the MPBS. They found that the highest field level was 1.5 V/m, corresponding to approximately 2.5% of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) guidelines for general public exposure (40 V/m to 60 V/m for GSM 800 MHz to 1800 MHz) (ICNIRP, 1998, 2009). Joseph et al. (2010) performed on-site measurements of RF from cellular MPBS at 30 locations in Stockholm, Sweden, and noted that the exposure levels were as high as 0.8 and 2.1 V/m for Long Term Evolution (2600 MHz) and Global System for Mobile Communications (900 MHz to 1800 MHz), respectively. The RF exposure from personal communication devices was generally higher than that emitted from radio and TV (maximum: 0.1 V/m to 0.3 V/m in a frequency range of 100 MHz to 830 MHz) (Joseph et al., 2010). Henderson and Bangay (2006) performed an exposure level survey of RF in 5 cities in Australia originating from MPBS antennas at distances over 50 m to 500 m from 60 MPBS. The highest recorded level from a single MPBS was 7.8×10^{-3} W/m^2 (1.7 V/m), also well below the general public exposure limits of the ICNIRP guidelines. In Taiwan, Li and Chen (2004) selected 6 elementary schools within 50 m from MPBS (exposed schools) and 9 unexposed schools to assess the RF levels potentially exposed to children. A total of 124 outdoor and 30 indoor locations selected at 6 exposed schools were measured for RF exposure level. The maximum outdoor RF level was 3.7 V/m. The mean level was 1.2 V/m. By contrast, the indoor RF levels were all less than 0.6 V/m (the minimum signal for detection) for the exposed schools. Data taken from the 177 outdoor locations at the 9 unexposed schools showed maximum and mean levels of 2.7 and 0.7 V/m, respectively. The maximum and mean indoor RF were both <0.6 V/m.

Most epidemiological health studies have focused on mobile phone use, only a few have investigated the cancer risk of people, in particular children, living in proximity to MPBS or other RF sources. Several previous studies have reported apparent cancer clusters in children constantly exposed to radio/TV, another source of RF (Maskarinec et al., 1994; Hocking et al., 1996; Dolk et al., 1997a, 1997b; Michelozzi et al., 2002). However, findings from these studies are difficult to interpret because of the small sample sizes as well as possible selection and reporting biases (Valberg et al., 2007; Schüz et al., 2009). Ha et al. (2007) investigated the risk of leukemia and brain cancer in children aged 15 years or less. The odds ratio (OR) for all types of leukemia was significantly increased at 2.15 among children who resided within 2 km of the nearest AM radio transmitter compared with those who resided more than 20 km from it. However, brain cancer was not associated with AM radio transmitter exposure. Merzenich et al. (2008) conducted a case-control study to explore the risk of leukemia in relation to high-power radio and TV broadcast towers in children aged 0 to 14 years. The OR for all types of leukemia was 0.86 (0.67, 1.11) when upper (≥95%/0.701 V/m) and lower (<90%/0.504 V/m) quantiles of the RF distribution were compared. The OR for all types of leukemia was 1.04 (0.65, 1.67) among children living within 2 km of the nearest broadcast transmitter compared with those living at a distance of 10–15 km. A recent UK study has reported no significant association between risk of early childhood cancers, including cancers of the brain and central nervous system, leukemia, and non-Hodgkin's lymphomas, and all cancers combined, as well as estimates of the mother's exposure to MPBS during pregnancy (Elliott et al., 2010). To date, little research has been conducted in children and adolescents. In addition, whether children are more susceptible to RF because the brain continues to develop during childhood and adolescence needs to be elucidated (WHO, 2010). Moreover, children are starting to be exposed to mobile phone handsets at a younger age. Hence, the World Health Organization (WHO) set a high-priority research requirement in its 2010 WHO Research Agenda for RF Fields (WHO, 2010), suggesting a need for further studies on children and adolescents with outcomes including cancer as well as behavioral and neurological disorders.

In accordance with the demand for mobile phone communication, more than 70,000 operational MPBS exist in Taiwan, with a land area of approximately 36,000 km^2, yielding a density of 2 MPBS per 1 km^2 (Chen and Li, 2010). We, therefore, conducted this population-based case-control study using national healthcare claims to investigate the association of RF exposure from MPBS and risks of all neoplasms, leukemia, and brain neoplasms in children.

2. Data sources and methods

2.1. Data source

Clinical data were retrieved from two datasets of the National Health Insurance Research Database (NHIRD) provided by the Bureau of National Health Insurance (BNHI). These datasets included Inpatient Expenditures by Admissions (IEA) and Registry for Beneficiaries (RB) that covers all Taiwan citizens. The NHIRD provides all inpatient and ambulatory care claims for approximately 96% of Taiwanese (Lu and Hsiao, 2003). Access to research data for 1998 to 2007 has been approved by the Review Committee of the National Health Research Institutes (NHRI).

Information on MPBS was obtained from the Taiwan National Communication Council (NCC), which is responsible for the approval of MPBS set up. A total of 71,185 MPBS have been operating in Taiwan from 1998 to 2007, and the information recorded for each MPBS included date of setup, date of removal (if any), power emitted (in watt), and address.

2.2. Study design and selection of cases and controls

This report comprised three population-based case-control analyses. Cases were identified from the IEA. In Taiwan, BNHI issues major illness/injury certificates to all patients who suffer from malignant neoplasm, and these patients are exempt from copayment to the NHI if they are admitted for the illness associated with the related malignancy (Chen et al., 2010). We recruited only those patients using major illness/injury certificates for the particular admissions to ensure further the accuracy of the diagnosis of childhood neoplasm. A total of 3481 children, aged 15 years or less, were admitted in 2003 to 2007 for all neoplasms (International Classification of Diseases-9th version-Clinical Modification (ICD-9-CM): 140–239), including 1346 cases of leukemia (ICD-9-CM: 204–208) and 503 cases of brain neoplasm (ICD-9-CM: 191). We linked these neoplasm patients to the IEA from 1998 to 2002 to exclude further those with neoplasm history prior to 2003 to ensure that our study subjects were newly diagnosed neoplasm patients during the recruitment period (i.e., 2003 to 2007). Such exclusion further reduced the number of childhood neoplasm patients to 2606, including 939 cases of leukemia and 394 cases of brain neoplasm. We linked each neoplasm patient to the RB for information on sex, date of birth, date of NHI enrollment, date of NHI policy termination (if any), and township.

Control subjects were selected from the RB. The numbers of insured children in 2003 to 2007 were 4,702,146; 4,522,049; 4,510,872; 4,385,806; and 4,280,843, respectively. We first excluded those children admitted for neoplasm (ICD-9-CM: 140–239) in 1998 to 2007. For each neoplasm patient, we then randomly selected 30 controls by matching the index case using year of birth and year of index case's neoplasm diagnosis. Age was calculated as the difference

in years between date of birth and date of neoplasm diagnosis (for cases) or July 1st in the year of the index case's diagnosis (for controls). The numbers of controls were 78,180; 28,170; and 11,820 for the case–control analyses of all neoplasm, leukemia, and brain neoplasm, respectively.

2.3. RF exposure metric

In Taiwan, the MPBS operated at a frequency of 800 MHz to 900 MHz and 1800 MHz to 2200 MHz. Because we did not have the information on RF exposure strength usually presented in V/m or W/m^2, a new exposure metric must be created by taking into account the power (in watt) and duration of operation (in year) of MPBS, and area (km^2) of a township. We first calculated the annual summarized power (ASP, in watt-year (WY)) for each MPBS annually from 1998 to 2007 from the product of duration of operation (in year) and real emitted power (in watt). Then, the annual power density (APD, WY/km^2) in each of the 367 townships in Taiwan was computed as a ratio of total ASP from all MPBS in a township to the area of that particular township. For each case, the RF exposure metric was estimated from the averaged APD for the five-year period (induction period) prior to the neoplasm diagnosis in the township where the subject lived at the time of neoplasm diagnosis. For those cases aged less than five years at the time of neoplasm diagnosis, the averaged APD was calculated for the induction period from the year of birth to the year of neoplasm diagnosis. For controls, we used July 1st in the year of the index case' neoplasm diagnosis to replace date of cancer diagnosis in creating the exposure metric for controls. The averaged APD was calculated using the following formula:

$$\left(\sum_{i=1}^{n}(y_i \times p_i)/A_i\right)/\text{No. of years for the induction period}$$

where n = number of MPBS in a township; y_i = years of operation for the ith MPBS during the induction period, $0<y_i\leq 5$; p_i = emitted power (in watt) from the ith MPBS; and A = area (km^2) of the ith township.

2.4. Potential confounders and statistical analysis

We first compared between cases and controls with respect to various characteristics of the study subjects. The RF exposure in relation to risks of childhood neoplasm was examined by multiple unconditional logistic regression models with the generalized estimation equation method (Burton et al., 1998), accounting for correlation in the error term because the study subjects could be clustered at the same township level. The potential confounders adjusted in the regression model included age, gender, calendar year of neoplasm diagnosis, urbanization level of township, and high-voltage (69/161/345 kV) transmission line (HVTL) density of the township. Adjustment for township urbanization in the regression model was performed because of possible urban–rural variations in health care accessibility and quality, as well as in accuracy of disease diagnosis noted in Taiwan (Chen et al., 2008). Additionally, HVTL density was adjusted because the power frequency magnetic field emitted from power lines have long been considered a risk factor for childhood cancer, especially for leukemia and, to a lesser extent, brain tumors (Kheifets et al., 2010a, 2010b, 2010c) Information on routes of HVTL in each township were obtained from the Geo-Information System (Li et al., 2007), which can also be used to estimate the area of each township. The HVTL density (in percentage) for each township was calculated using the ArcView 9.0 (ESRI, Redlands, CA), as the ratio of the areas within 100 m away from HVTL (km^2) to the total area of the township (km^2) (Ger et al., 2007; Li et al., 1998a, 1998b). All statistical analyses were performed with SAS (version 9.1.3; SAS Institute, Cary, NC). A P value <0.05 was considered statistically significant.

3. Results

Table 1 shows the characteristics of cases of all neoplasm, leukemia, and brain neoplasm, as well as their corresponding controls. For each of the three case–control analyses, cases and birth year-matched controls were also comparable with regard to year of diagnosis (cases) or selection (controls), urbanization level, and density of HVTL in living areas, but were dissimilar relating to gender with slight boy dominance in the three case–control samples.

Covariate-adjusted OR of all neoplasm associated with per 10 WYs/km^2 increase in a 5-year average of APD (OR = 1.02, 95% confidence interval (CI) = 0.96 to 1.08) was essentially close to 1.0. However, an elevated covariate-adjusted OR (1.13, 95% CI = 1.01 to 1.28) was observed for ≥median exposure (167.02 WYs/km^2). The adjusted OR for the highest tertile exposure was not significantly elevated (1.10, 95% CI = 0.90 to 1.33) (Table 2).

Cases of leukemia and corresponding controls were only slightly different in the 5-year averaged power density (499.7 $WYs/km^2 \pm$ 917.0 WYs/km^2 vs. 553.1 $WYs/km^2 \pm 990.2$ WYs/km^2), representing an OR of 0.97 (95% CI = 0.87 to 1.08) in relation to per 10 WYs/km^2 increase in power density after selected potential confounders were considered. The 5-year average of APD ≥ median value of controls (168.67 WYs/km^2) was associated with an increased risk of leukemia with an adjusted OR of 1.23 (95% CI = 0.99 to 1.52). No elevated ORs were noted for the highest tertile exposure (Table 3).

Table 4 shows the OR of brain neoplasm in relation to various exposure measures. The mean annual power density was higher for cases of brain neoplasm than for controls (596.2 $WYs/km^2 \pm$ 1096.2 WYs/km^2 vs. 527.5 $WYs/km^2 \pm 951.0$ WYs/km^2). However, such difference yielded no significant increase in covariate adjusted OR associated with per 10 WYs/km^2 increase in exposure. Additionally, risk of brain neoplasm was only slightly increased for ≥median exposure (168.07 WYs/km^2) or ≥2nd tertile exposure (392.86 WYs/km^2), with an adjusted OR of 1.14 (95% CI = 0.83 to 1.55) and 1.14 (95% CI = 0.70 to 1.85), respectively.

4. Discussion

4.1. Main findings

This study noted that Taiwanese children with higher-than-median exposure of RF potentially emitted from MPBS were at significantly increased risk of all neoplasms combined. Although there were also positive associations between MPBS-emitted RF power density and risks of brain neoplasm and leukemia in children, such associations did not reach statistical significance.

4.2. Comparison of results from previous studies

Only a few studies have been conducted to investigate the association between cancer and MPBS, most of which have focused on adults. Meyer et al. (2006) conducted an ecological study investigating the cancer risk among 177,428 persons living in 48 municipalities in Bavaria, Germany between 2002 and 2003 in relation to the coverage of MPBS. The study classified exposure into three levels, determined according to the transmission duration of each MPBS. They found no indication of an overall increase in cancer incidence in municipalities belonging to the highest exposure class (Röösli et al., 2010). An Israeli study compared the cancer incidence rate between 622 residents living in proximity to a cell-phone transmitter station for 3 years to 7 years and the whole nation's population, and found that the exposed residents are at 4.15 times higher risk of cancer incidence than the entire population (Wolf and Wolf, 2004). The Bavaria and Israeli studies differed in study

Table 1
Characteristics of case and control series according to selected neoplasm.

Variables	All neoplasm				Leukemia				Brain neoplasm			
	Control		Case		Control		Case		Control		Case	
	n	%	n	%	n	%	n	%	n	%	n	%
Year of diagnosis/selection												
2003	15990	20.5	533	20.5	6150	21.8	205	21.8	2490	21.1	83	21.1
2004	17460	22.3	582	22.3	6060	21.5	202	21.5	2550	21.6	85	21.6
2005	15930	20.4	531	20.4	6240	22.2	208	22.2	2430	20.6	81	20.6
2006	15870	20.3	529	20.3	5130	18.2	171	18.2	2520	21.3	84	21.3
2007	12930	16.5	431	16.5	4590	16.3	153	16.3	1830	15.5	61	15.5
Age (years)												
<5	26130	33.4	871	33.4	11070	39.3	369	39.3	2760	23.4	92	23.4
5–9	20400	26.1	680	26.1	8340	29.6	278	29.6	4200	35.5	140	35.5
10–15	31650	40.5	1055	40.5	8760	31.1	292	31.1	4860	41.1	162	41.1
M ± SD	7.6 ± 4.7		7.8 ± 4.7		6.8 ± 4.6		7.0 ± 4.3		8.1 ± 4.3		8.2 ± 4.3	
Gender												
Boy	41055	52.5	1465	56.3	14802	52.5	545	58.2	6139	51.9	216	54.8
Girl	37125	47.5	1138	43.7	13368	47.5	393	41.8	5681	48.1	178	45.2
Urbanization												
High	22359	28.6	730	28.0	8310	29.5	247	26.3	3333	28.2	115	29.1
Middle	22203	28.4	781	30.0	7803	27.7	285	30.4	3451	29.2	116	29.4
Low	33618	43.0	1095	42.0	12057	42.8	407	43.3	5036	42.6	163	41.5
Density of HVTL[a]												
High	44329	56.7	1489	57.1	15804	56.1	521	55.4	6786	57.4	224	56.9
Middle	21890	28.0	742	28.5	7972	28.3	283	30.2	3297	27.9	109	27.6
Low	11961	15.3	375	14.4	4394	15.6	135	14.4	1737	14.7	61	15.5
Total	78180	100.0	2606	100.0	28170	100.0	939	100.0	11820	100.0	394	100.0

[a] HVTL = High Voltage Transmission Lines; High: ≧8.54%; Middle: 3.12–<8.54%; Low: 0–<3.12%.

design and length of observation, and no information on RF power density was considered in the analysis, which may have contributed to the dissimilarities in their findings. The null association between RF exposure from MPBS and risk of cancer was proven by a previous study that analyzed the annual incidence rates of glioma and meningioma in four Nordic countries from 1973 to 2007. This study has shown no change in incidence trends from 1998 to 2003, the time when possible associations between mobile phone use and cancer risk would be informative with an induction period of 5 years to 10 years (Deltour et al., 2009). Additionally, some recent studies have also reported that the increased use of mobile phones has not led to a noticeable change in the trend in brain cancer incidence rates in Nordic countries (Deltour et al., 2012), the UK (de Vocht et al., 2011), and the US (Inskip et al., 2010).

Most of the studies for childhood cancer risk associated with RF exposure have been focused on the RF emitted from various unmovable sources, such as radio/TV transmission antenna and MPBS. In the 1990s and early 2000s, several studies have explored residential proximity to radio/TV transmitters and risk of childhood leukemia (Maskarinec et al., 1994; Hocking et al., 1996; Dolk et al., 1997a, 1997b; Michelozzi et al., 2002) and brain cancer (Hocking et al., 1996). Although some studies have observed significantly increased risk (approximately 2-fold) of leukemia in children living in the vicinity of transmitters (Hocking et al., 1996; Dolk et al., 1997b), these studies were all based on a small number of cases, and no systematic RF measurements have been made in the study areas. This condition makes the interpretation of the study findings difficult and precludes firm conclusions. Moreover, some findings of these preliminary studies were not supported by subsequent studies that updated the original studies. For example, McKenzie et al. (1998) reexamined results from a report by Hocking et al. (1996) and noted that the excess risk was mainly limited to one local government area within the studied region. Cooper et al. (2001) updated several earlier studies by Dolk et al. (1997a, 1997b) by collecting cancer data from recent years (1987 to 1994). The updated study not only failed to replicate the earlier finding that a decreasing risk exists with distance for leukemia in adults, but also included too few childhood leukemia cases (26 in total), to reach conclusions on childhood leukemia risk. Two case–control studies improved the exposure

Table 2
Odds ratio of all neoplasm in relation to RF exposure density (WYs/km^2) in the residential township of the study subject.

Exposure measures	Control (n = 60810)	Case (n = 2046)	Crude estimate			Adjusted estimate[a]		
	Mean (SD)[b]/ n (%)	Mean (SD)[b]/ n (%)	OR[b]	95% CI[b]	*P*	OR[b]	95% CI[b]	*P*
Per 10 WYs/km^2 increase	539.4 (971.9)	539.9 (972.9)	1.00	0.96–1.05	0.981	1.02	0.96–1.08	0.540
Dichotomous classification[c]								
≥Median	30666 (50.4%)	1068 (52.2%)	1.07	0.98–1.17	0.115	**1.13***	**1.01–1.28**	**0.048**
<Median	30144 (49.6%)	978 (47.8%)	1.00			1.00		
Tertile classification[d]								
≥2nd Tertile	20770 (34.1%)	708 (34.6%)	1.04	0.94–1.16	0.425	1.10	0.90–1.33	0.360
≥1st–<2nd Tertile	19845 (32.6%)	678 (33.2%)	1.04	0.94–1.17	0.444	1.02	0.89–1.17	0.796
<1st Tertile	20195 (33.3%)	660 (32.3%)	1.00			1.00		

The bold emphasis and asterisk symbol indicate $p<0.05$.
[a] Adjustment was made for calendar year, age, gender, high-voltage transmission line density, and urbanization of township.
[b] SD = standard deviation; OR = odds ratio; CI = confidence interval; WYs = Watt-years.
[c] Median = 167.02 WYs/km^2.
[d] 1st Tertile = 91.65 WYs/km^2; 2nd Tertile = 392.86 WYs/km^2.

Table 3
Odds ratio of leukemia in relation to RF exposure density (WYs/km^2) in the residential township of the study subject.

Exposure measures	Control (n = 20894)	Case (n = 721)	Crude estimate			Adjusted estimate[a]		
	Mean (SD)[b]/ n (%)	Mean (SD)[b]/ n (%)	OR[b]	95% CI[b]	*P*	OR[b]	95% CI[b]	*P*
Per 1 SD WYs/km^2 increase	553.1 (990.2)	499.7 (917.0)	0.94	0.87–1.02	0.154	0.97	0.87–1.08	0.604
Dichotomous classification[c]								
≥Median	10413 (49.8%)	368 (51.1%)	1.05	0.90–1.22	0.525	1.23	0.99–1.52	0.052
<Median	10481 (50.2%)	353 (48.9%)	1.00			1.00		
Tertile classification[d]								
≥2nd Tertile	7291 (34.9%)	231 (32.1%)	0.86	0.72–1.03	0.100	0.82	0.59–1.13	0.171
≥1st–<2nd Tertile	6689 (32.0%)	235 (32.6%)	0.95	0.80–1.14	0.598	0.85	0.68–1.07	0.229
<1st Tertile	6914 (33.1%)	255 (35.3%)	1.00			1.00		

[a] Adjustment was made for calendar year, age, gender, high-voltage transmission line density, and urbanization of township.
[b] SD = standard deviation; OR = odds ratio; CI = confidence interval; WYs = Watt-years.
[c] Median = 168.67 WYs/km^2.
[d] 1st Tertile = 92.16 WYs/km^2; 2nd Tertile = 392.86 WYs/km^2.

assessment using propagation models to estimate total RF exposure from radio/TV transmitters inside the home of each study child, but they still found no association with childhood leukemia (Ha et al., 2007; Merzenich et al., 2008). One of the common concerns for the previous studies of RF and childhood cancer is that those studies appeared to suffer from limited sample sizes.

A recent UK registry-based case–control study has investigated the risk of early childhood cancers associated with the mothers' exposure to RF from and proximal to MPBS during pregnancy (Elliott et al., 2010). This study recruited a total of 1397 cases of childhood cancer aged 0 to 4 years and 5588 sex- and birth date-matched controls. With such a large sample size that effectively reduced random variation in risk estimates frequently encountered by most previous studies (Auvinen et al., 2006), this UK study still showed no difference in mean distance of registered address at birth from an MPBS, (1107 m vs. 1073 m), including the total power output of MPBS within 700 m of the address (2.89 kW vs. 3.00 kW).

Similar to the findings from most previous studies, our study found no significantly increased risk of leukemia or brain cancer in children with potentially higher RF exposure from MPBS. However, findings in our study and those reported in previous ones may not be fairly comparable because not all previous studies investigated RF exposure from MPBS. Additionally, study samples may differ with respect to lifestyle, which may contribute to substantial variations in exposure. For example, in addition to MPBS, the utilization of cell phones may considerably contribute to the overall RF exposure in older children, but not in very young children. Moreover, various methods have been used to determine RF exposure level, including personal dosimetry (Cooper et al., 2004) and calculated level (Baste et al., 2010). Although we attempted to quantify the individual's RF intensity exposure based on an ecological level, not this method or the previous ones are considered the correct measure biologically, if any, related to occurrence of human cancer.

4.3. Methodological considerations

Our study has several methodological strengths. First, the NHI database is population-based and highly representative, causing little possibility of selection bias. The BNHI performs experts' review of 50 to 100 randomly selected ambulatory and inpatient claims to ensure the accuracy of claim files (Bureau of National Health Insurance, 2000). The reviews are conducted every four months annually. Therefore, information obtained from the NHIRD is believed to be complete and accurate. By the end of 1996, BNHI had contracted with 97% of hospitals and clinics all over the nation, and 99% of the total Taiwanese population has already enrolled in the program (Lu and Hsiao, 2003). There is also a small likelihood of non-response study subjects because all information was ascertained from the NHI database without reliance on study subject's recall. Second, one of the major advantages of using insurance claim datasets in epidemiological research is the easy accessibility of the longitudinal records for a large sample of geographically dispersed patients (Jollis et al., 1993). Third, given that the diagnostic procedures of childhood neoplasm can be dependent on medical resources and physicians' behavior, adjustment of geographic area and urbanization level reduced geographic- and urbanization-related biases. Moreover, a previous study has indicated little variation in the accuracy of diagnosis for childhood leukemia (Li et al., 1998b). Finally, we excluded patients

Table 4
Odds ratio of brain neoplasm in relation to RF exposure density (WYs/km^2) in the residential township of the study subject.

Exposure measures	Control (n = 11820)	Case (n = 394)	Crude estimate			Adjusted estimate[a]		
	Mean (SD) [b]/ n (%)	Mean (SD) [b]/ n (%)	OR[b]	95% CI[b]	*P*	OR[b]	95% CI[b]	*P*
Per 1 SD WYs/km^2 increase	527.5 (951.0)	596.2 (1096.6)	1.07	0.97–1.18	0.196	1.09	0.95–1.25	0.230
Dichotomous classification[c]								
≥Median	4923 (49.7%)	174 (51.9%)	1.09	0.88–1.36	0.434	1.14	0.83–1.55	0.426
<Median	4969 (50.3%)	161 (48.1%)	1.00			1.00		
Tertile classification[d]								
≥2nd Tertile	3387 (34.2%)	121 (36.1%)	1.09	0.77–1.32	0.525	1.14	0.70–1.85	0.599
≥1st–<2nd Tertile	3212 (32.5%)	106 (31.6%)	1.01	0.84–1.42	0.964	1.03	0.73–1.45	0.875
<1st Tertile	3293 (33.3%)	108 (32.3%)	1.00			1.00		

[a] Adjustment was made for calendar year, age, gender, high-voltage transmission line density, and urbanization of township.
[b] SD = standard deviation; OR = odds ratio; CI = confidence interval; WYs = Watt-years.
[c] Median = 168.07 WYs/km^2.
[d] 1st Tertile = 93.98 WYs/km^2; 2nd Tertile = 392.86 WYs/km^2.

with all kinds of malignancies prior to the neoplasm diagnosis to obtain relatively accurate information of incident cancer cases, which also greatly reduced the likelihood of Neyman bias (Delgado-Rodriguez and Llorca, 2004).

Several limitations were noted in our study. First, exclusive reliance on the claim data might have resulted in potential disease misclassification bias. Claim data included the medical information only for people who sought treatments at clinics or hospitals. Thus, the control group might still have been mixed up with new onset or undiagnosed childhood neoplasm. Additionally, considering that we only selected neoplasm patients with major illness/injury certificates for the precision of diagnosis of malignancy, we might have missed some patients who had been waiting for the pathological diagnosis and had not received major illness/injury certificates. However, neoplasm is a major clinical end-point, and nearly all neoplasm patients should be hospitalized especially under the coverage of NHI program that greatly removes the economic barrier for poor or socially deprived individuals. Furthermore, previous studies have shown little evidence for the geographic variation in neoplasm under-diagnosis in children in Taiwan (Li et al., 1998b), which provided reassurance that the areas with a higher density of MPBS were also unlikely to have a higher or lower rate of neoplasm under-diagnosis. Therefore, the potential disease misclassification bias should be minimal in our study.

Second, the main source of bias involved in the present study is likely associated with measures of RF exposure. The assessment of RF exposure considered the RF emitted from MPBS. In addition to MPBS, a number of RF sources may have co-existed in the environment, including radio and television broadcasting, as well as an explosive growth in wireless communications infrastructure and services, such as wireless local area networks, wireless fidelity, and RF identification devices (Valberg et al., 2007; Röösli et al., 2010). Failure to perform a complete assessment of all RF sources may result in certain degrees of RF exposure misclassification, which is likely to be a random error that usually distorts the results by attenuating real effects (when they exist), provided that they affect the compared groups in a similar fashion (i.e., non-differential error or exposure misclassification) (Copeland et al., 1977; Dosemeci et al., 1990; Gordis, 2000). Moreover, our study also failed to distinguish mobile phone RF exposures from exposure directly from MPBS, given that a high density of base stations in areas with a high frequency of mobile telephone communication is expected. A recent survey has reported that 45.0% of grade 5 children are mobile phone users, and the figure increases to 71.7% for grade 9 children (Chen and Li, 2010). Such cell phone use prevalence rate is generally lower than those reported from many Western nations (Schüz, 2005; Söderqvist et al., 2007). Failure to consider the exposure from cell phone further makes the specific interpretation of our findings difficult. In this study, we do not have any information on the use of mobile phones of each individual child. Some of these subjects were old enough to use mobile phones. However, the exposure levels might not be too high if the children do send messages but do not speak over the phones.

Although our study attempted to integrate the power density emitted by MPBS into exposure assessment, which is dissimilar to many previous studies on childhood leukemia (Maskarinec et al., 1994; Ha et al., 2007) and brain cancer (Ha et al., 2007) that relied solely on “distance from sources of RF” to determine exposure level for study subjects, our approach was still subject-to-exposure misclassification given that the exposure measure did not consider within-township variability. Another drawback of using ecological RF exposure data as a proxy for individual exposure is that the distributions of RF exposure might be very unusual. In Table 3, we noted an increased OR for exposure ≥median exposure, but the ORs for the two upper tertiles were reduced. We examined the data and noted a sharp increase in proportion of cases at 50%–<55%. We may observe a higher RF exposure in cases than in controls when the RF exposure is dichotomously characterized [i.e., ≥50% (i.e., median) vs. <50%]. However, when the RF exposure was categorized with tertiles, the proportion of cases in the 1st tertile (i.e., <33.3%) was much greater than that of controls, leading to a reduced OR.

Third, data analyzed in this study are claims of beneficiaries whose personal identification numbers have been encrypted before they can be accessed for research purpose. In addition, we have only the information of township where the beneficiaries lived at the time of diagnosis. These make it impossible for us to use geo-coded models or the use of personal dosimeters in performing exposure assessment. Furthermore, given that the NHI dataset included only the residential area where the beneficiaries lived at the time of admission, we were unable to track the complete information on the subject's residences, which might also entail certain degrees of exposure misclassification. Again, such exposure misclassification was likely to occur equally in both cases and controls. Fourth, although we adjusted the density of HVTL and urbanization level of a township in the regression model, we could not determine other known risk factors for childhood cancer (e.g., family socioeconomic characteristics) or for leukemia (air pollutants and virus infection) and brain cancer (occupational exposure to organic solvents of parents) specifically, which might have also confounded the study results. However, an earlier study has reported a close relationship between urbanization and population movement (mixture) in Taiwan (Li et al., 1998b). Urbanization is expected to be highly related to traffic and family socioeconomic characteristics. HVTL density was adjusted because the power frequency magnetic field emitted from power lines has been considered a risk factor for childhood leukemia, and to a lesser extent, for brain cancer (Kheifets et al., 2010a; Mezei et al., 2008).

5. Conclusion

In conclusion, our study does not indicate a significant association of MPBS-emitted RF at levels typically encountered in people's everyday environment with risks of brain neoplasm and leukemia in children. Although risk of overall neoplasm is elevated in children with higher-than-median RF exposure, the magnitude of risk estimate was small, and further causal interpretation of such positive link is limited because of a lack of specificity for the selected end-point. The results noted in this study may also occur due to several methodological limitations. Additionally, given a limited number of studies on neoplasm risk of children, we suggest a need for additional epidemiological studies of young children and adolescents, considering that their developing brain and other tissues might be more susceptible than those of adults to potential effects of low-level exposures to RF (Kheifets et al., 2005). Where data are scarce, the absence of evidence of harm should not necessarily be interpreted as evidence that no harm exists. We also suggest that further research should be performed with improved exposure assessment methods considering other sources of RF, and the direct information on exposure of fetus should be collected for studies of early childhood neoplasm.

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