

Childhood leukemia and magnetic fields in Japan: A case-control study of childhood leukemia and residential power-frequency magnetic fields in Japan

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Residential power-frequency magnetic fields (MFs) were labeled as a possible human carcinogen by the International Agency for Research on Cancer panel. In response to great public concern, the World Health Organization urged that further epidemiologic studies be conducted in high-exposure areas such as Japan. We conducted a population-based case-control study, which covered areas inhabited by 54% of Japanese children. We analyzed 312 case children (0–15 years old) newly diagnosed with acute lymphoblastic leukemia (ALL) or acute myelocytic leukemia (AML) in 1999–2001 (2.3 years) and 603 controls matched for gender, age and residential area. Weekly mean MF level was determined for the child's bedroom. MF measurements in each set of a case and controls were carried out as closely in time as possible to control for seasonal variation. We evaluated the association using conditional logistic regression models. The odds ratios for children whose bedrooms had MF levels of 0.4 μ T or higher compared with the reference category (MF levels below 0.1 μ T) was 2.6 (95% CI = 0.76–8.6) for AML + ALL and 4.7 (1.15–19.0) for ALL only. Controlling for some possible confounding factors did not alter the results appreciably. Even an analysis in which selection bias was maximized did not fully explain the association. Most of the leukemia cases in the highest exposure category had MF levels far above 0.4 μ T. Our results provided additional evidence that high MF exposure was associated with a higher risk of childhood leukemia, particularly of ALL.

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Key words: residential magnetic fields; childhood leukemia; population-based; case-control study; Japan

Exposure to residential power-frequency magnetic fields (MFs) has been suspected to increase the risk of childhood leukemia, although the risk suggested by the first report¹ has not consistently been supported by the following ones.^{2–10} Recently, however, pooled analyses conducted by Ahlbom *et al.*¹¹ used geometric means of MF levels and showed that the estimated summary relative risk was 2.00 (95% CI = 1.27–3.13) when 0.4+ μ T was compared with < 0.1 μ T. Another pooled analysis by Greenland *et al.*¹² used arithmetic means of MF levels and showed that the Mantel-Haenszel odds ratio comparing 0.3+ μ T with < 0.1 μ T was 1.7 (95% CI = 1.2–2.3).

Still, the small number of cases in high-dose ranges remains one of the limitations of these pooled analyses, and the causal inference remains tenuous because of little evidence from animal experiments and lack of appropriate biologic models. Thus, the World Health Organization recommended conducting one or more epidemiologic studies to evaluate the risk with more subjects exposed to high MF levels in 1999,¹³ although the International Agency for Research on Cancer (IARC) rated the power-fre-

quency MF as a possible human carcinogen in 2002¹⁴ mainly based on the above finding by the pooled analyses.

Thus, the present nationwide case-control study of childhood leukemia was conducted in Japan, where high MF exposures were expected to be more common than in the previously studied countries. This expectation was derived from Japan's high population density and the proximity of residences to electric power transmission lines (which refers not only to high-voltage power lines but also to distributing transmission lines to the residences) and other facilities as major sources of high residential MF levels, although detailed data on residential MF levels and exposures were not available when the present study was initiated in 1999.

Compared to the previous studies, this study is characterized by more precise week-long exposure measurements, shorter intervals between the diagnosis and the MF measurements both in cases and controls, as well as a rigorous selection bias assessment. We believe this study, the first elaborately conducted study from non-Western countries, will add substantial evidence to the body of scientific knowledge concerning this controversial issue.

Material and methods

The present study was approved by the Ethics Committee for Human Studies of the National Institute for Environmental Studies, Tsukuba, Japan.

Subjects

We identified newly diagnosed childhood leukemia cases through the following 5 major children's cancer study groups in Japan: Tokyo Children's Cancer Study Group (TCCSG), Children's Cancer and Leukemia Study Group (CCLSG), Tohoku Children's Leukemia Study Group, Japan Association of Childhood Leukemia Study (JACLS) and Kyushu/Yamaguchi Children's Cancer Study Group (KYCCSG). Participating hospitals in these groups numbered 245 in total. More than half of the hospi-

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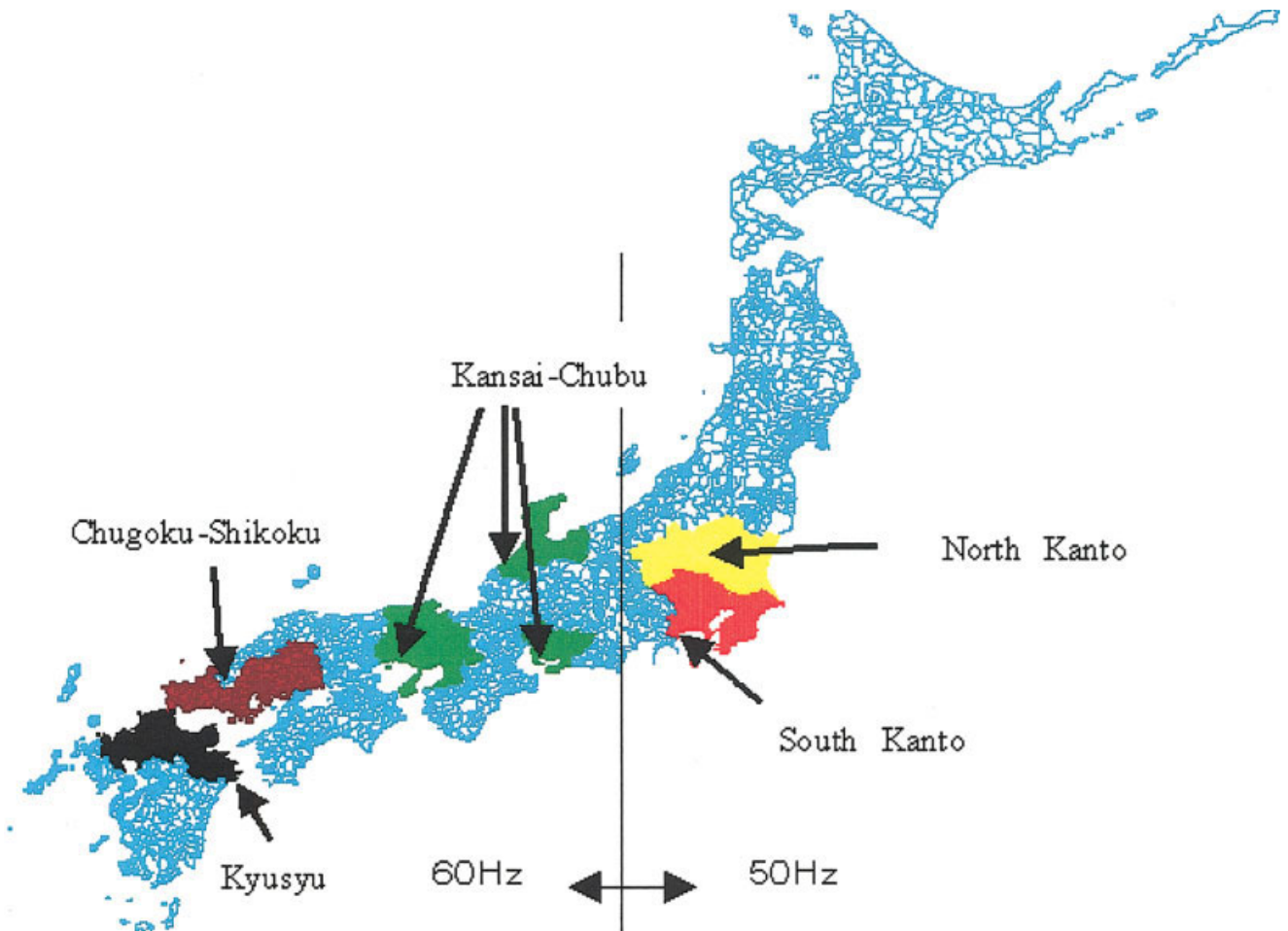


FIGURE 1 – Catchment area.

tals were located in the areas with megalopolis. Our cases were restricted to acute lymphoblastic leukemia (ALL) and acute myelocytic leukemia (AML) for the sake of comparability with the previous studies.^{6,8,11,12} The diagnoses of ALL and AML were made on the basis of morphologic, immunologic, as well as cytogenetic and molecular genetic features of the peripheral blood and bone marrow aspirate. Children with diseases or conditions known to increase the risk for leukemia were excluded from this study. These conditions included chromosomal abnormalities such as Down's syndrome, DNA fragility syndromes such as Fanconi's anemia and immunodeficiency syndromes such as Wiscot-Aldrich syndrome.

Although the case ascertainment through the 5 groups virtually covered the entire nation, we restricted our study area, or catchment area, to 5 regions, including Tokyo, Nagoya, Kyoto, Osaka and Kitakyushu metropolitan areas (Fig. 1). This was because other areas than the catchment area were mainly sparsely populated and we expected that the proportion of residents with high levels of MF exposure would be very low. The catchment area consisted of 18 prefectures in the 5 regions covering 10.7 million (53.5%) of the total 20.0 million children aged 0–15 years in Japan.¹⁵

Requests for participation in the interview survey were sent to 781 (ALL + AML) cases living in the catchment area through the children's physicians; 381 families agreed to participate. Thus, the participation rate for the overall cases was $381/781 = 0.49$. Sixty out of the 381 (AML + ALL) cases who initially agreed were excluded. Among the 60 cases, 25 were excluded due to moving

after diagnosis and 35 were excluded due to measurement failure. The reasons for the MF measurement failure were the following: instrument trouble occurred in the houses of 5 cases, and 30 cases changed their minds and stopped participating.

Once informed consent for participation was obtained from the patient's family, we randomly selected controls from the Japanese resident registration system in the catchment area by matching for gender, age ($\pm 25\%$ for age < 4 years; ± 1 year for age above 4 years), region and population size of the municipality (4 classes). We selected 10 control candidates for each case to achieve 3 matched controls, because the participation rate for mail surveys in Japan is usually less than 30%.¹⁶ Multiple letters requesting participation were sent until 3 controls were set for each case. In total, 3,833 candidates in the catchment area were requested to participate and 1,097 (28.6%) agreed. Among them, interview and MF measurements were completed for 634 subjects. We excluded 23 controls due to incomplete MF measurements. Further, we did not interview the remaining 440 control candidates since the number of controls to be interviewed was reduced to 2 for each case later in the study because of the difficulty of arranging interview schedules for a set of 1 case and 3 matched controls within a short study period.

Interviews

One or 2 trained interviewers were allocated for each of the 5 regions in the catchment area. The questionnaire was based on that used in the National Cancer Institute study⁶ and modified for this Japanese study. In brief, the modified questionnaire consisted of

TABLE I – RISK OF ALL + AML WITH COVARIATES LISTED BELOW

Bedroom MF level (μ T)	All subjects included	All subjects included (nighttime measurements)	Subjects lived in current residences for more than 6 months
Below 0.1	1.00	1.00	1.00
0.1–0.2	0.93 (0.51–1.71)	0.97 (0.52–1.79)	0.90 (0.47–1.72)
0.2–0.4	1.08 (0.51–2.31)	1.08 (0.47–2.47)	1.09 (0.50–2.38)
Above 0.4	2.77 (0.80–9.57)	2.87 (0.84–9.88)	3.20 (0.87–11.7)

Covariates: father's education and mother's education.

¹Time-weighted average for 1 week, except for the middle column, for which only nighttime (19:00–06:00) measurements were used.

demographic profiles, medical history of family members, history of moves (from conception to leukemia diagnosis), type of residence, mother's education, child's history of vaccinations, mother's and child's histories of electric appliance use, mother's history of X-ray examination during pregnancy, drug use, smoking, alcohol drinking, pesticide and other agricultural chemical uses, as well as mother's and father's employment history. We interviewed one of the parents of the cases/controls; the interviews were predominantly with mothers (97.8% for cases and 96.2% for controls).

MF and other measurements

Two types of MF measurements were conducted: 1-week-long continuous measurement at 30-sec intervals with the EMDEX-Lite (40 Hz to 1 kHz; Enertech, Cambell, CA) in the child's bedroom and 5-min-long spot measurements with the EMDEX-II (40 to 800 Hz; Enertech) at several points inside and outside of the house. The study by Friedman *et al.*¹⁷ as well as ours¹⁸ showed that a 24-hr bedroom measurement was a good surrogate for 24-hr personal exposure.

Thus, we selected the MF level in the child's bedroom as a measure of residential exposure. However, instead of 24-hr mean levels, we used weekly mean levels, since residential MF levels in many of the residences examined were lower during weekends compared with weekdays, especially among residences where indoor MF levels highly correlated with outdoor levels generated by nearby power lines. It was also apparent that those weekly variations were reflecting those in the power supply through the lines.

It has been suggested that MFs generated by transmission lines may show a seasonal variation, depending on the extent of air conditioning use.¹⁹ In order to reduce a possible bias due to seasonal variation of MF levels, the dates of MF measurements in controls and their cases were arranged as closely in time as possible; the mean difference between case and controls within each set was 2.6 ± 13.0 days.

Residential history

Based on the residential history of the families, we obtained the length of stay at the current residence where the MF levels were measured. This information allowed us to consider possible exposure misclassification due to moving.

Statistical analyses

Among the subjects with MF measurements and interviews conducted, 9 cases lost their matched controls and 31 controls lost their matched cases. We excluded these 40 subjects. The remaining 312 cases (251 ALLs, 61 AMLs) and 603 controls (495 ALLs, 108 AMLs) were subjected to conditional logistic regression analyses. The association between residential MF exposure and childhood leukemia was measured in odds ratio (OR). We used PHREG procedure of the PC-SAS (version 8.2; SAS Institute, Tokyo, Japan) and computed ORs and their 95% confidence intervals.

Because of the possibility of an inverse dose-response relation even in the low-exposure range,²⁰ we first evaluated the association between ALL risk and MF levels with 0.05 μ T intervals using

the method of Greenland.²¹ Since this evaluation did not indicate any necessity for finer categorization, the MF level was then categorized with cut-points of 0.1, 0.2 and 0.4 μ T for the sake of comparability with the pooled analyses.^{11,12}

A possible confounding effect was examined by adding the potential confounders (Table I) to the logistic regression model as covariates. In some models, we restricted the subjects to those who had lived at their present residence for more than 6 months.

Evaluation of selection bias

Because we had expected low participation proportions for both cases and controls, evaluation of the selection bias was planned in the study protocol. We evaluated the selection bias in the following 4 different ways.

GIS-based evaluation. Differential participation, if any, probably comes from the suspicion of high MF exposure in case families. It is natural to assume that their suspicion of high exposure comes from living in close proximity to the high-voltage power lines, not from the actual MF measurements. Thus, for the cases and the controls, we evaluated the difference in the distribution of the distance from the closest power line among cases and controls by the participation status.

For controls, we estimated the distribution of the distance from the residence to the closest power line by the participation status in the study. We were able to calculate the distance for all the control candidates even if they did not agree to participate because their names and addresses in the Japanese registration system are open to the public. As for the cases, we could calculate the distribution of the distance for those who agreed to participate in the study. Also, we obtained maps indicating power lines from the 10 power companies in Japan. From these data, we calculated the distance between a subject's house and the closest power line (22–500 kV) using a geographic information system (GIS) software (ArcInfo; ESRI, Tokyo, Japan). If the maps showed that a power line was located within 100 m from the house, the distance was actually measured with a laser-beam distance meter (Yardage Pro Model 20-1000; Bushnell, Overland Park, KS) for ascertainment in the field.

Possible influence of selection bias on relative risk parameter. In addition to the above evaluation, we evaluated the possible influence of selection bias on the ORs due to differential participation by sensitivity analysis. Detailed explanation can be found in the Appendix. In brief, we evaluated whether or not the possible most extreme scenario, in which all nonparticipant cases have low exposure, could reduce the apparent positive risk to the null.

Subgroup investigation on participation among cases. For case candidates identified through TCCSG, the largest children's cancer study group among the 5 groups, we investigated the reasons for nonparticipation by asking the physicians. By this investigation, we could evaluate whether or not there was a systematic bias in participation among subjects by exposure levels.

Matching failure. Some subjects were excluded from the conditional logistic regression analyses due to matching failure, *i.e.*, the situation in which a case-control set loses the case or the entire controls due to insufficiency of necessary data. To evaluate the effect of this matching failure, we did unconditional logistic

TABLE II – SOME DESCRIPTIVE CHARACTERISTICS OF CASES AND CONTROLS

Total number ¹	ALL				AML			
	Cases		Controls		Cases		Controls	
	n = 251	%	n = 495	%	n = 61	%	n = 108	%
Sex								
Male	146	58.2	287	58.0	32	52.5	56	51.9
Female	105	41.8	208	42.0	29	47.5	52	48.2
Age at diagnosis (years)								
< 2	28	11.2	63	12.7	10	16.4	16	14.8
2–3	69	27.5	133	26.9	12	19.7	17	15.7
4–5	43	17.1	85	17.2	10	16.4	22	20.4
6–9	58	23.1	115	23.2	14	23.0	30	27.8
≥ 10	53	21.1	99	20.0	15	24.6	23	21.3
Father's education								
≤ junior high school	18	7.3	24	4.9	6	9.8	2	1.9
Senior high school	88	35.8	154	31.2	27	44.3	26	24.1
≥ college/university	140	56.9	316	63.9	28	45.9	80	74.0
Mother's education								
≤ junior high school	18	7.2	21	4.2	4	6.6	1	0.9
Senior high school	102	40.6	180	36.4	26	42.6	40	37.0
≥ college/university	131	52.2	294	59.4	31	50.8	67	62.0
Mother's history during pregnancy								
Smoking								
Yes	33	13.2	42	8.5	7	11.5	9	8.3
No	217	86.8	452	91.5	54	88.5	99	91.7
Alcohol drinking								
Yes	67	26.8	152	30.8	16	26.2	36	33.3
No	183	73.2	342	69.2	45	73.8	72	66.7
Passive smoking								
Yes	109	43.4	189	38.3	31	50.8	40	37.0
No	142	56.6	305	61.7	30	49.2	68	63.0
Type of residence								
Single-family house	141	56.2	283	57.2	32	52.5	67	62.0
Apartment	106	42.2	205	41.4	27	44.3	41	38.0
Length of stay at current house (months)								
< 6	16	6.4	27	5.4	3	4.9	12	11.1
6–11	23	9.2	31	6.3	3	4.9	5	4.6
≥ 12	212	84.5	437	88.3	55	90.2	91	84.3

¹Individual variable totals may not equal the total number of cases and controls due to missing values.

regression analyses, including those who were excluded from the conditional analyses.

Results

Basic profiles of subjects

Selected basic profiles of the subjects are summarized in Table II. Mothers of the ALL cases had lower educational levels and a higher proportion of smokers (including passive smokers) during pregnancy than those of the controls. Mothers of AML cases had the same distributions of the attributes except for passive smoking, which was more prevalent among AML controls' mothers than among AML cases' mothers. The mean time between the diagnosis and the MF measurements was 13.3 ± 5.8 months for ALL + AML cases and 13.2 ± 5.6 months for controls. (Controls do not have dates of diagnosis; the case's diagnosis date was assigned to the corresponding controls.)

One-week MF measurements and spot measurements

Table III shows the correlations between 1-week MF measurements and spot measurements. The 1-week measurements had high correlations with the spot measurements of detached houses, whereas the correlations with the spot measurements of condominiums were a little lower.

Risk of MF levels for childhood leukemia

As shown in Table IV, leukemia risk was associated with the highest MF category, $0.4+ \mu\text{T}$. The OR for ALL + AML was 2.56 (95% CI = 0.76–8.58) and that for ALL was 4.67 (95% CI = 1.15–19.0) against the reference category (MF levels below $0.1 \mu\text{T}$). As shown in Table I, controlling for the potential con-

found factors or using nighttime (from 19:00 to 06:00) measurement only did not alter the ORs substantially, and restricting the subjects to those who lived for more than 6 months in a given residence yielded an even higher OR for the highest MF category.

When the distance from the power lines was used as a surrogate for residential MF level, the ORs for ALL for 50–100 m and < 50 m were 1.61 (95% CI = 0.88–2.95) and 3.06 (95% CI = 1.31–7.13), respectively, against the reference category (100+ m). The corresponding ORs for AML were 3.11 (95% CI = 0.71–13.6) and 1.25 (95% CI = 0.11–14.9).

Variations in MF levels

The large hour-to-hour and day-to-day variations in MF levels were observed especially among those with high exposure levels as shown in Figure 2. Specifically, the weekend levels were lower than the weekday levels. This weekday-weekend difference was also observed for the subjects with lower exposure levels, although the difference was smaller; the average MF level for weekends was $0.051 \mu\text{T}$ and that for weekdays was $0.054 \mu\text{T}$.

Profiles of highly exposed subjects

There were only 6 out of 312 cases and 5 out of 603 controls exposed to more than $0.4 \mu\text{T}$ MF. All high-exposure cases and 3 controls are for ALL and no cases and 2 controls are for AML. Table V shows the sex and age at diagnosis, and Figure 2 shows bedroom MF level for the cases and the controls in the highest-exposure category. Most of ALL cases in this group had MF levels much higher than $0.4 \mu\text{T}$. The ages at diagnosis of the cases were mostly less than 7 years old.

TABLE III – CORRELATIONS BETWEEN 1-WEEK MF MEASUREMENTS AND SPOT MEASUREMENTS

	One-week measurement (all houses)	Spot measurement (detached houses)						Spot measurement (condominiums)	
		BR1	BR2	OC1	OC2	OC3	OC4	Entrance	Window
One-week	1.000	0.938 < 0.0001	0.826 < 0.0001	0.914 < 0.0001	0.910 < 0.0001	0.874 < 0.0001	0.895 < 0.0001	0.712 < 0.0001	0.632 < 0.0001
	915	914	913	530	526	502	477	375	372
BR1	0.938 < 0.0001	1.000	0.894 < 0.0001	0.891 < 0.0001	0.880 < 0.0001	0.863 < 0.0001	0.891 < 0.0001	0.735 < 0.0001	0.726 < 0.0001
	914	914	913	530	526	502	477	374	371
BR2	0.826 < 0.0001	0.894 < 0.0001	1.000	0.868 < 0.0001	0.856 < 0.0001	0.852 < 0.0001	0.878 < 0.0001	0.444 < 0.0001	0.415 < 0.0001
	913	913	913	529	525	501	476	374	371
OC1	0.914 < 0.0001	0.891 < 0.0001	0.868 < 0.0001	1.000	0.937 < 0.0001	0.842 < 0.0001	0.886 < 0.0001		
	530	530	529	530	519	492	470		
OC2	0.910 < 0.0001	0.880 < 0.0001	0.856 < 0.0001	0.937 < 0.0001	1.000	0.894 < 0.0001	0.839 < 0.0001		
	526	526	525	519	526	492	463		
OC3	0.874 < 0.0001	0.863 < 0.0001	0.852 < 0.0001	0.842 < 0.0001	0.894 < 0.0001	1.000	0.882 < 0.0001		
	502	502	501	492	492	502	470		
OC4	0.895 < 0.0001	0.891 < 0.0001	0.878 < 0.0001	0.886 < 0.0001	0.839 < 0.0001	0.882 < 0.0001	1.000		
	477	477	476	470	463	470	477		
Entrance	0.712 < 0.0001	0.735 < 0.0001	0.444 < 0.0001					1.000	0.558 < 0.0001
	375	374	374					375	372
Window	0.632 < 0.0001	0.726 < 0.0001	0.415 < 0.0001					0.558 < 0.0001	1.000
	372	371	371					372	372

The 3 numbers in each cell are correlation coefficient, *p*-value, and number of pairs. BR1 (bedroom 1) and BR2 are 2 places in the bedroom, the former being the center of the room and the latter being at the head of the sleeping child. OC1 (outside corner 1) through OC4 are 4 corners of the houses. Window is the one opposite to the entrance.

TABLE IV – RISK OF ALL + AML AND ALL AND CHILD'S BEDROOM MF MEASUREMENTS CONDITIONAL LOGISTIC REGRESSION ANALYSES WITH NO COVARIATE

	ALL + AML			ALL		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Bedroom MF level (μT) ¹						
Below 0.1	276	542	1.00	223	447	1.00
0.1–0.2	18	36	0.91 (0.50–1.63)	14	29	0.87 (0.45–1.69)
0.2–0.4	12	20	1.12 (0.53–2.36)	8	16	1.03 (0.43–2.50)
Above 0.4	6	5	2.56 (0.76–8.58)	6	3	4.67 (1.15–19.0)
Total	312	603		251	495	

¹Time-weighted average for 1 week.

Evaluation of selection bias: GIS-based evaluation and sensitivity analysis

No association was found between participation status of controls and proximity to power lines; according to Appendix Table II, the participation proportion for < 50, 50–100, 100–300 and 300+ m were 0.15, 0.16, 0.16 and 0.16, respectively (*p* = 0.98).

Assuming the worst possible case scenario in which all highly exposed cases participated and cases not participating had low exposure levels (details are explained in the Appendix), we obtained 1.84 for the lowest possible odds ratio for subjects exposed to MF levels 0.4+ μT against levels < 0.1 μT .

Evaluation of selection bias: investigation of nonparticipation among cases

Among the letters sent to the cases identified through TCCSG, 40% were not delivered to patients' families, and 12% were delivered but the families did not agree to participate. Therefore, the participating proportion among requests delivered was 80%. The reasons for nondelivery included patients' serious medical conditions and failure to contact the families by the physicians due to various reasons, such as a long interval between our request to the physician and the patient's visit to the hospital.

Evaluation of selection bias: matching failure

The unconditional logistic regression analysis of ALL showed that the OR for the 0.4+ μT category was 4.45 (95% CI = 1.10–17.9) controlling for age, sex and population size of the city. Substantial difference was not observed for different combination of potential confounders. The value of OR was not substantially different from the results of the conditional logistic regression analysis.

Discussion

Our study found a statistically significant association between high residential MF levels (0.4+ μT) and childhood ALL in Japan. The dose-response pattern and magnitude of the ORs of ALL + AML in the present study were generally in good agreement with those of published pooled analyses.^{11,12} A meaningfully increased risk was observed in none of the studies up to the level of 0.4 μT , and the ORs for 0.4+ μT against < 0.1 μT were 2.00 (95% CI = 1.27–3.23) in the study by Ahlbom *et al.*¹¹ and 1.60 (95% CI = 1.03–2.48) in the study by Greenland *et al.*¹²

Our study has several methodologic advantages over the previous studies. First, MF levels were measured for an entire week. Although Friedman *et al.*¹⁷ reported that 24-hr bedroom spot MF

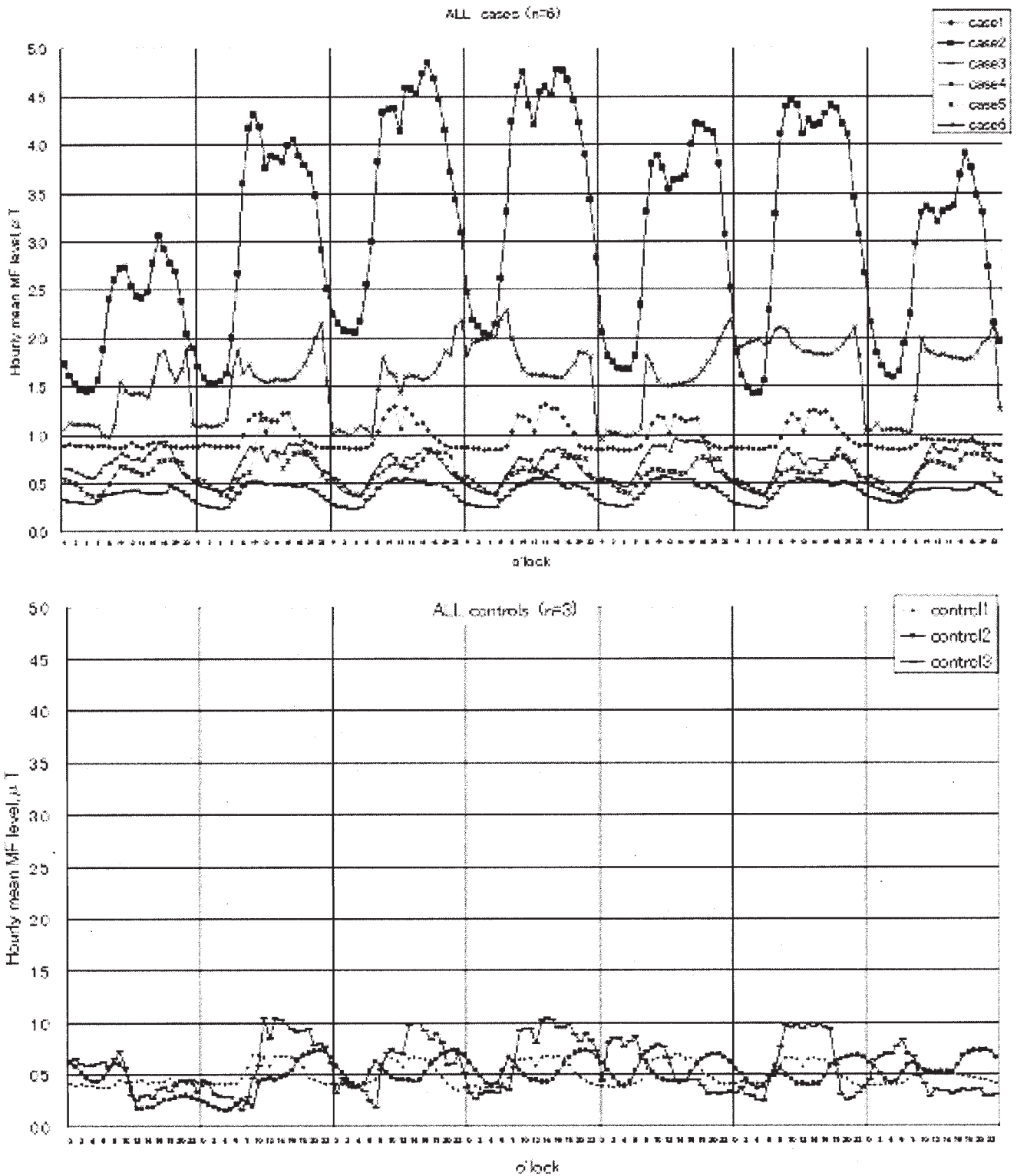


FIGURE 2 – Hourly mean bedroom MF level in the highest exposure category.

level used in the previous study⁶ was a useful predictor of personal dosimetry measurements, the hour-to-hour variation and day-to-day variation as demonstrated for the high bedroom MF level group may raise concern about measurement errors and possible biases. In this sense, our results using 1-week-long bedroom MF level as a measure of exposure are more precise and less biased.

To show this point, we evaluated the fluctuation of the OR estimates (adjusted for mother's and father's education) using 1-day MF level by restricting the MF measurements only to the first day, the second day, . . . , or the seventh day of the weeklong measurements; the results showed that the point estimates of the OR comparing 0.4+ μT with < 0.1 μT ranged from 1.48 to 2.61. Although

TABLE V – SEX AND AGE AT DIAGNOSIS OF ALL CASES AND CONTROLS IN THE CATEGORY OF BEDROOM MF LEVEL > 0.4 μ T

Sex	Type	Age at diagnosis (years)
Controls		
Male	ALL	2.4
Female	ALL	3.1
Male	ALL	11.5
Female	AML	9.5
Male	AML	11.1
Cases		
Female	ALL	2.2
Male	ALL	5.0
Male	ALL	5.7
Male	ALL	6.2
Male	ALL	6.4
Male	ALL	12.0

the results are considered to be consistent, we might have obtained incidentally a lower or higher OR estimate if we had used 1-day MF level, instead of 1-week MF level. Second, the MF measurements for cases were taken close in time to those for matched controls. The short interval between the measurement dates for a case and matched controls should have reduced the seasonal variation in MF measurements between the case and controls. Third, the interval between the diagnosis and the interview was even shorter than the previous study that tried to reduce the interval.⁶ With a longer interval, we would expect a lower correlation between the MF levels measured in the study and the actual MF levels that might have caused the disease in the past.

As we expected at the study outset, the participation rate for the mail questionnaire survey for controls was low (28.6%), and this may be an important source of concern. In Japan, this level of response rate is not uncommon. Since people seldom encounter mail surveys for real scientific studies, people may be weary of commercial direct mails that pretend to be mail surveys. Whatever the reason for the poor participation rate, the key question is whether the differential participation led to significantly biased results regarding the relation with exposure, and hence the rigorous analysis of selection bias was performed in this study. We found no difference in participation proportion between those controls living close to the power line and those living not close to the power line by GIS-based analysis. Unfortunately, the same analysis could not be conducted for cases because the information was not available for cases that did not participate in the study. However, as shown in the results, low participation rate in cases (0.49) was due not to the cases' intentional rejection of the study, but to the low accessibility to patients through physicians. Although the low accessibility may still be related to exposure level, our sensitivity analysis showed the minimum true OR for subjects with

0.4+ μ T MF is 2.32 and the maximum true odds ratio under the null hypothesis is 2.04 if selection bias is taken into consideration. Although the actual OR suffers from random variation, this calculation shows that the selection bias *per se* cannot fully explain our positive finding.

In addition, our bias evaluation, such as controlling for potential confounding factors including socioeconomic factors like mothers' education, the subject restriction by residence history and the unconditional logistic regression analyses, revealed no substantial difference in the results.

Another limitation of our study is the lower than expected proportion of subjects who were exposed to high MF exposures. Possible reason for the lower proportion seems to be related to the following characteristics in Japan: towers for high-voltage overhead transmission lines are higher (taller) than other countries in general; the power lines have been paired such that the MFs of the lines cancel out (this system was adopted in the 1970s).

In conclusion, the present study, the first large-scale case-control study conducted outside of Europe and the United States, based on weekly measured MF levels in children's bedrooms, showed an increased risk of MF level above 0.4 μ T for ALL + AML or ALL only, but not for the lower MF levels. We consider the above results were not due to bias alone, although these may be due to chance.

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Appendix

Sensitivity analysis of selection bias on relative risk parameter

The data layout for formulations for the bias evaluation is shown in Appendix Table I, which shows the counterfactual situation in which all the case and control candidates participate, as well as the actual situation in the present study. The true odds ratio estimate (OR_t) and observed odds ratio estimate (OR_a) in this instance would be calculated as

$$OR_t = \frac{AD}{BC} \tag{1}$$

$$OR_a = \frac{ad}{bc}$$

The OR_t would be rewritten as follows using Equation 1 and participation proportions:

$$OR_t = \frac{(a/P_{CaH})(d/P_{CoL})}{(b/P_{CoH})(c/P_{CaL})} \tag{2}$$

$$= OR_a \frac{P_{CaL}}{P_{CaH}} \cdot \frac{P_{CoH}}{P_{CoL}}$$

where P_{CaH} is the participation proportion for the cases with high exposure, P_{CaL} that for the cases with low exposure, P_{CoH} that for the controls with high exposure and P_{CoL} that for the controls with low exposure. That is, $\hat{P}_{CaH} = a/A$, $\hat{P}_{CoH} = b/B$, $\hat{P}_{CaL} = c/C$ and

APPENDIX TABLE I - DATA LAYOUT FOR FORMULATIONS OF THE BIAS EVALUATION

Exposure level	Cases	Controls
Situation in which all the eligible subjects are included		
High	A	B
Low	C	D
Observed situation in which part of the eligible subjects are included		
High	a	b
Low	c	d

APPENDIX TABLE II - DISTRIBUTION OF THE DISTANCE FROM THE CLOSEST POWER LINE

Distance from power line	Cases	Controls
Situation in which all the eligible subjects are included (column percent in parentheses)		
< 50 m		190 (5.0)
50-100 m		231 (6.1)
100-300 m		735 (19.4)
300+ m		2,626 (69.4)
Total	791 (100)	3,782 (100.0)
Observed situation (column percent in parentheses)		
< 50 m	20 (6.4)	29 (4.8)
50-100 m	25 (8.0)	37 (6.1)
100-300 m	55 (17.6)	115 (19.1)
300+ m	212 (67.9)	422 (70.0)
Total	312 (100.0)	603 (100.0)

Some subjects were excluded because their GIS information was not available.

APPENDIX TABLE III - SELECTION BIAS EVALUATION WITH SOME OBTAINED DATA: ALL AS AN EXAMPLE

Exposure level	Cases	Controls
Observed situation reconstructed from Table 2-1, ALL panel ¹		
High (0.4+ μT)	6	3
Low (0.4 μT <)	245	492
Total	251	495
Situation in which all the eligible subjects are included		
High (0.4+ μT)	A	B
Low (0.4 μT <)	C	D
Total	626	B + D
Situation with $P_{CaH} = 1$, i.e., $A = a = 6$		
High (0.4+ μT)	6	B
Low (0.4 μT <)	620	D
Total	626	B + D

¹ $OR_a = 4.02.$

$\hat{P}_{CoL} = d/D$. Therefore, sensitivity analysis can be conducted by evaluating OR_t with Equation 2 and some obtained results.

Appendix Table II shows the distribution of the distance from the closest power line by selection status. The controls studied had almost identical distance distribution as those who were requested to participate, i.e., there was no selection bias among the control candidates. This observation implies that $P_{CoH} = P_{CoL}$ can be assumed for controls, and Equation 2 can be reduced to

$$OR_t = OR_a \frac{P_{CaL}}{P_{CaH}} \tag{3}$$

We tried to evaluate the minimum value of OR_t in the sensitivity analysis in order to maximize the bias. The above formula says OR_t is the smallest when $P_{CaH} = 1$ (meaning that all the cases who were exposed to the high MF levels were included in the study). If this value is applied to the ALL panel of Table 2-1, then $a = A = 6$ for Appendix Table III. Since the total number of ALL cases we requested to participate was 626, then $C = 626 - 6 = 620$, as shown in Appendix Table III. From these data, $\hat{P}_{CaL} = c/C = 245/620 = 0.40$. Since OR_a for the ALL was 4.02 (using Appendix Table III), substituting 0.40 for \hat{P}_{CaL} into Equation 3 yields the minimum OR_t being 1.61. In the same line of reasoning, minimum observable OR_a 2.53 under the null hypothesis of OR_t being unity. Hence, OR_t should be greater than unity when OR_a 2.53. Although the above analysis neglects matching, doing so did not appear to influence the estimation of ORs in our study, as mentioned in the main body of the article.