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A cohort study on adult hematological malignancies and brain tumors in relation to magnetic fields from indoor transformer stations

Muhammad Waseem Khan [a,b], Jukka Juutilainen [a], Anssi Auvinen [c,d], Jonne Naarala [a], Eero Pukkala [c,e], Päivi Roivainen [a,d,*]

[a] Department of Environmental and Biological Sciences, University of Eastern Finland, Kuopio, Finland
[b] Department of Biotechnology, Balochistan University of Information Technology, Engineering & Management Sciences, Quetta, Pakistan
[c] Unit of Health Sciences, Faculty of Social Sciences, Tampere University, Tampere, Finland
[d] STUK - Radiation and Nuclear Safety Authority, Helsinki, Finland
[e] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

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ABSTRACT

Extremely low frequency (ELF) magnetic fields (MF) have been classified as possibly carcinogenic. This classification was mainly based on studies indicating increased risk of leukemia in children living near power lines. Increased risks of adult hematological malignancies and brain tumors have also been reported, but the results are mixed. We assessed incidence of adult hematological malignancies and brain tumors associated with residential MF exposure. All cohort members had lived in buildings with indoor transformer stations (TS). MF exposure was assessed based on apartment location. Out of the 256,372 individuals, 9,636 (165,000 person-years of follow-up) living in apartments next to TSs were considered as exposed. Associations between MF exposure and neoplasms were examined using Cox proportional hazard models. The hazard ratio (HR) for MF exposure $\geq$ 1 month was below one for most hematological neoplasms (HR for any hematological neoplasm: 0.75; 95% CI: 0.54–1.03), and decreased with increasing duration of exposure (HR for exposure $\geq$ 10 years: 0.47; 95% CI: 0.22–0.99). However, the HR for acute lymphocytic leukemia (ALL) was 2.86 (95% CI: 1.00–8.15), based on 4 exposed cases; the risk increased with duration of exposure (HR for exposure $\geq$3 years: 3.61; 95% CI: 1.05–12.4) and was particularly associated with childhood exposure (2 exposed cases, HR for exposure during the first two years of life: 11.5; 95% CI: 1.92–68.9). The HR for meningioma was 0.46 (95% CI: 0.19–1.11), with no evidence of exposure-response gradient with increasing duration of exposure. The HR for glioma was 1.47 (95% CI: 0.84–2.57). The hypothesis of a positive association between ELF MFs and adult hematological malignancies was supported only for ALL. The results suggested decreased rather than increased risk of most hematological neoplasms.

1. Introduction

Extremely low frequency (ELF) magnetic fields (MFs) occur wherever alternating current electric power is generated, transmitted, distributed or used. In 2002, the International Agency for Research on Cancer (IARC) classified ELF MFs as "possibly carcinogenic to humans", mainly based on epidemiological studies reporting an association between exposure to ELF MFs and childhood leukemia (IARC, 2002). Causality of this association is still unclear (Amoon et al., 2018; Juutilainen et al., 2018).

Epidemiological studies on ELF MFs and adult cancers have mainly focused on occupational exposure. Reviews and meta-analyses of these studies indicate that workplace MF exposure may be associated with small increases in risk estimates of leukemia and brain cancer (Huss et al., 2018; Kheifets et al., 2008a; 2008b; WHO, 2007). There is limited evidence that also lymphoma may be associated with occupational exposure to ELF MFs (Huss et al., 2018; Koeman et al., 2014). However, drawing conclusions from these studies is difficult for several reasons. Quality of exposure assessment is a major challenge in occupational MF epidemiology, and the risk estimates may have been affected by considerable misclassification of exposure. Furthermore, the results do not show clear evidence of an exposure-response relationship, cancer

* Corresponding author. University of Eastern Finland Department of Environmental and Biological Sciences P.O. Box 1627, FI-70211, Kuopio, Finland.
E-mail address: paivi.roivainen@uef.fi (P. Roivainen).

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subtypes do not show a consistent pattern between studies, improved exposure assessment methods are not associated with increased risk estimates, and risk estimates in new meta-analyses tend to be lower than in previous ones (Kheifets et al., 2008b).

Relatively few studies have addressed adult cancers in relation to residential exposures to ELF MFs. In some of these studies, exposure was assessed using questionnaires or interviews to collect information regarding use of electrical appliances (Kleinerman et al., 2005; Mutnick and Muscat, 1997), which is prone to recall bias when conducted after disease occurrence. In many studies, exposure assessment was based on proximity to electrical installations, usually power lines (Baldi et al., 2011; Coleman et al., 1989; Lowenthal et al., 2007; McDowall, 1986). Distance alone is a poor proxy of MF exposure, involving substantial misclassification and complicating interpretation of the findings of studies that rely on distance alone (Maslanyj et al., 2009). Although some studies have reported increased risks for leukemia (or subtypes of leukemia) and brain cancer, the evidence is not consistent, even in studies with higher quality exposure assessment methods, such as residential MF measurements and calculation of residential MFs based on distance from power lines, current in the power lines and their structural characteristics (Elliot et al., 2013; Fazzo et al., 2009; Feychting et al., 1997; Klaeboe et al., 2005; Tynes and Haldorsen, 2003; Verkasalo et al., 1996). Low prevalence of high MF exposure and hence lack of precision is a general limitation of the studies that have investigated cancer risks near power lines – using a cutoff point higher than 0.2 μT has generally not been possible in adult cancer studies that have involved measured or calculated MFs. This is a serious limitation, given that childhood cancer seems to be associated with fields greater than 0.3 or 0.4 μT, with little or no evidence of increased risk below these levels (Ahlbom et al., 2000; Greenland et al., 2000). Moreover, like in childhood cancer studies (Ahlbom et al., 2000; Greenland et al., 2000), selection bias and confounding remain as potential explanation for the results of many adult leukemia and brain cancer studies. Overall, the conclusion by Ahlbom et al. (2000) concerning childhood cancer studies is also valid for studies on adult cancer: further studies will be helpful only if selection bias and confounding can be adequately addressed, and if exposure over 0.4 μT is sufficiently common.

In this paper, we report a cohort study on adult hematological malignancies and brain tumors among residents of buildings with indoor transformer stations. We have previously constructed a database of such buildings and their residents and it provides an opportunity to study possible health effects of ELF MFs using a high-quality study design that avoids the main limitations of previous studies (Khan et al., 2019). Previous validation studies have shown that the ELF MF exposure of the residents can be assessed with low exposure misclassification based solely on apartment location and field levels exceeding 0.4 μT are common in apartments directly above the transformers (Hareuveny et al., 2011; Huss et al., 2013; Ilonen et al., 2008; Röösli et al., 2011; Thuroczy et al., 2008). Exposed and referent individuals live in the same buildings, which minimizes variation in potential confounding factors such as socioeconomic status and other environmental exposures. Furthermore, selection bias can be avoided: all eligible subjects can be included without contacting the residents or obtaining access to the residences.

2. Methods

2.1. Study population and exposure assessment

The study cohort was identified using the Database of Finnish Buildings with Indoor Transformer Stations (DaFBITS). Details of the database, compiled by our research group, have been described elsewhere (Khan et al., 2019). Briefly, information of buildings with indoor transformer stations was obtained from electricity distribution companies and information of individuals who have lived in these buildings from the Population Information System, which is maintained by the Finnish Digital and Population Data Services Agency. The computer-based Population Information System started in 1971 and has extensive records of full residential history from 1983 to date. Information on earlier years is available for a limited number of individuals, and the follow-up started on the earliest available date for each individual. Personal identity codes can be used for record linkage to Cancer Registry only from January 1, 1967, so this was the earliest date for the start of follow-up. All individuals included in the study were aged 18 or above at the end of study (December 31, 2016) and had lived in the buildings included in DaFBITS. The Ethical Committee of the University of Eastern Finland reviewed and approved the study protocol in January 2017 (Statement 4/2017). As the study was conducted based on register data alone without any contact with the study subjects, no informed consents were required according to the Finnish regulations.

Exposure assessment was based on the information compiled for DaFBITS. All apartments of the buildings included in DaFBITS were classified into five ELF MF exposure categories (Khan et al., 2019, Fig. 1; Table S1) according to their location in relation to the transformer room, which is always located on the ground floor or basement. The transformers convert 10 kV or 20 kV to the supply voltage (230 V), and one transformer typically serves several buildings. The power generation frequency in Finland is 50 Hz. In the present study, a person was classified as "exposed", if she/he had been living for at least one month in an apartment located directly above the transformer room (category 1 in DaFBITS) or in an apartment sharing a wall with the transformer room (category 2). These were all on ground or first floors. Person-years produced by individuals who had resided in apartments sharing only a corner with the transformer room (classified as an intermediate exposure category 3 in DaFBITS) were excluded, as this is a small group and measurements of exposure level are not available. Disease risk was estimated also for individuals who had lived for at least one month in apartments on the first or ground floor but not adjacent to the transformer room (category 4 in DaFBITS) to assess possible confounding associated with living on the first or ground floor. Hereafter, this group will be called "first or ground floor residents". The reference group consisted of individuals who had resided for at least one month in apartments on any other floor than the first or ground floors of the building (category 5 in DaFBITS). Follow-up was started one month (in the main analysis) after an individual had moved into the apartment that defined her/his exposure, and continued until the end of the study (December 31, 2016), emigration from Finland, death or to the date of diagnosis of the outcomes studied (Table 1), whichever occurred first. Reference group members who later moved into an "exposed" or a first or ground floor apartment were followed as referents until the move and were changed to the relevant group after the move. If the transformer was installed in the building later than the start of residence, follow-up was started one month after the installation of transformer. For those individuals who were less than 18 years one month after the start of residence or the date of the installation of transformer, follow-up started from the 18th birthday.

A total of 203,663 individuals, of whom 97,410 (47.8%) were men and 106,253 (52.2%) women, were included in the main analyses (Table 2). The median age of the individuals at the start of the residence was 26.2 years, interquartile range (IQR) from 20.5 to 35.9. Altogether 9,636 individuals (4.7% of the cohort in main analysis) were included in the exposed group, while 194,027 individuals (95.3%) had been living in reference apartments. The total person-years of follow up were 165,240 for the exposed residents, 3,323,413 for the referents and 877,994 for the first or ground floor residents. In the main analysis, the median person-years of follow-up was 15.3 years (IQR from 7.0 to 25.5) for the cohort, 15.6 years (IQR from 7.3 to 25.6) for the exposed group, 15.2 years (IQR from 7.0 to 25.5) for the reference group and 14.9 years (IQR from 7.0 to 24.5) for the first or ground floor residents. Person-years were also calculated for different age intervals (Table S2). Median duration of residence varied from 2.4 to 3.0 years in the apartment categories included in the analyses (Table 2).

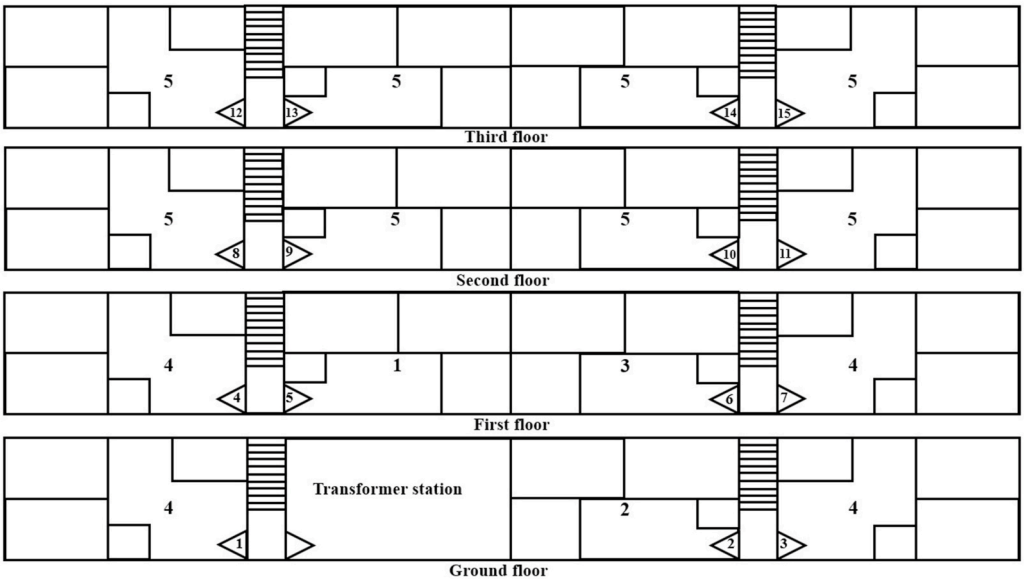

Fig. 1. Schematic representation of a building with an indoor transformer station showing the classification of apartments in relation to the transformer station. 1 = apartment located above the transformer station; 2 = apartment sharing a wall with the transformer station; 3 = apartment sharing a corner with the transformer station; 4 = apartment located on the same floor as apartment in category 1, 2 or 3; 5 = apartment located on any other floor of the building.

Table 1
Neoplasms included in the study and their codes according to the 10th revision of the International Classification of Diseases (ICD 10).

Neoplasm type	ICD 10 code	Total number of cases
Any hematological neoplasms	C81 – C96	1,102
All types of leukemia	C91 – C95	287
Lymphoid leukemia	C91	135
Acute lymphocytic leukemia	C91.0	32
Chronic lymphocytic leukemia	C91.1, 91.4	103
Myeloid leukemia	C92	134
Acute myeloid leukemia	C92.0, 92.3, 92.4, 92.5	88
Chronic myeloid leukemia	C92.1	37
Lymphoma	C81–C88	656
Hodgkin lymphoma	C81	97
Non-Hodgkin lymphoma	C82–C85, C88	559
Multiple myeloma	C90	157
Glioma[a]	C71.0 - C71.9	196
Meningioma[a]	C70.0, D32, D42.9	240

[a] International Classification of Diseases for Oncology (3rd edition) coding was used to classify the morphology of tumors.

2.2. Outcome information and data analysis

The cohort was linked to Finnish Cancer Registry. The unique personal identifiers assigned to each Finnish resident were used as the key in a deterministic linkage. Finnish Cancer Registry contains population-based data on cancer incidence starting from the year 1953 (Pukkala et al., 2018). Completeness of registration is high (about 99%) for all sites; registrations of non-solid tumors being less complete than that of solid tumors but still high (Pukkala et al., 2018). The outcomes considered were adult (diagnosis at age 18 or above) hematological malignancies and brain tumors. The complete list of neoplasm types included in the study is reported in Table 1. Information on possible dates of death or emigration from Finland was obtained from the Population Information System. The last day of follow-up was December 31, 2016.

The analyses were planned *a priori*. The only exception was a complementary visual analysis (see below). Cox proportional hazard models were used for estimating hazard ratios (HR) with 95% confidence intervals (95% CI) for the associations of residential ELF MF exposure with selected neoplasms. Time on study (in years) was used as the time scale in the analyses. Results were adjusted for gender and age at the start of residence. The Cox analyses were performed using IBM SPSS Statistics Version 25 (IBM Corp, Armonk NY, USA). If there were no exposed cases, the Cox model did not produce a useful upper limit for the 95% CI. In such cases, mid-P exact 95% CI for the conditional maximum likelihood estimate of rate ratio was calculated using Open Source Epidemiologic Statistics for Public Health version 3.01 (www.OpenEpi.com).

Our exposure classification does not produce estimates of exposure levels for each study subject in terms of magnetic flux density. Therefore, to assess existence of exposure-response relationship, we

Table 2
Characteristics of the study individuals according to extremely low frequency magnetic field exposure categories.

Apartment Category	1	2	3	4	5
Number of individuals	8,944	692	3,196	52,709	194,027
Gender			NI[a]		
Male	4,354	344		25,472	92,712
Female	4,590	348		27,237	101,315
Median age at the start of residence (years) (5th – 95th percentile)	25.7 (0.35–58.6)	25.9 (0.04–58.1)	NI[a]	26.2 (0.83–59.8)	26.3 (1.06–59.5)
Median duration of residence (years) (5th – 95th percentile)	2.7 (0.29–20.0)	3.0 (0.29–21.5)	NI[a]	2.4 (0.26–18.8)	2.5 (0.26–20.1)
First year in study: Median (5th – 95th percentile)	1995 (1974–2014)	1997 (1979–2013)	NI[a]	1997 (1974–2014)	1997 (1973–2014)

1 = apartment located above the transformer room; 2 = apartment sharing a wall with the transformer room; 3 = apartment sharing a corner with the transformer room, 4 = apartment located on the same floor as apartment in category 1, 2 or 3; 5 = apartment located on any other floor of the building.
[a] NI = not included in the present study.

investigated the relationship between duration of residence (as a proxy for duration of residential MF exposure) and risk of disease. Cox models were restricted to individuals who had resided in the buildings for <3 years, 3 to <10 years or ≥10 years. Follow-up in these analyses was started after the specified minimum duration of residence. If this was before the 18th birthday of the individual, follow-up was started from the 18th birthday. Linear regression weighted by sample size was used to examine trends over these exposure categories, with median duration of exposure as the exposure value in each category (Brownstein and Cai, 2019).

The findings of a study on adult lympho- and myeloproliferative diseases (Lowenthal et al., 2007), together with the studies reporting elevated risk of childhood leukemia, suggest that ELF MF exposure during the early years of life might be important also for induction of adult cancers. To study the impact of age at the start of exposure, Cox models were run for individuals who had resided in the buildings at different periods of life. The periods considered were first 2 years of life, ages from 2 to <15 years, and ages ≥15 years. After seeing the results of this analysis, we performed a complementary analysis to visualize the impact of age at the onset of exposure. The number of cases in the exposed and reference groups was calculated for each 5-year class of age at the start of residence in the buildings. The contribution of these cases to the observed final age-standardized incidence rates was examined by plotting the apparent incidence rate in each 5-year class (incidence rate that takes into account only persons with specified age at the start of residence) cumulatively as a function of age at the start of residence.

As a sensitivity analysis, we excluded person-years of category 2 apartments from the exposed group. No MF measurement data for this apartment category are available in Finland, but they were included in the main analysis based on studies in other countries (Huss et al., 2013; Röösli et al., 2011). The MF levels are likely to be lower in these apartments than in category 1 apartments, because category 2 apartments share only a wall with the transformer room. As the second sensitivity analysis, we included the first or ground floor residents in the reference group.

3. Results

3.1. Incidence rates

The truncated age-standardized incidence rate (cases per 100,000 person-years; follow-up started at 18 years) was in most cases lower in the exposed individuals than in the reference group (Table 3). Only the incidence rates of acute lymphocytic leukemia (ALL) and glioma were higher among the exposed individuals than among the referents.

3.2. Overall hazard ratios

The HRs for both all hematological neoplasms combined and all leukemias were below unity, indicating that the risk of these neoplasms was lower in the exposed than in the reference group (Table 4). The MF-related reduction in risk of total leukemia mainly reflected a very low risk estimate for myeloid leukemia. Among myeloid leukemias, the HRs of both acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) were low (only one AML case and no CML cases in the exposed group). With regard to lymphoid leukemia, the risk of ALL was elevated 2.86-fold among the MF-exposed individuals, while the HR for chronic lymphocytic leukemia (CLL) was reduced. The HR for all types of leukemia other than ALL was 0.43 (95% CI: 0.18–1.04). The HRs were below unity also for lymphomas. The HR for multiple myeloma was only slightly above 1.00. The HR for glioma was 1.47, while that for meningioma was 0.46-fold among the MF-exposed individuals.

The risk estimates were not materially affected by exclusion of the category 2 apartments from the "exposed" group (Table S3) or by inclusion of category 4 apartments into the reference group (Table S4). The HR for ALL increased in both sensitivity analyses, to 3.06 (95% CI: 1.07–8.73) in the first (Table S3) and to 3.52 (95% CI: 0.99–12.5) in the second (Table S4) sensitivity analysis. The HR for glioma, in contrast, decreased in both sensitivity analyses. The decreased HRs for lymphoma and meningioma were accentuated in the second sensitivity analysis. The HRs for individuals living in first or ground floor apartments (category 4) were all close to 1.00 (from 0.82 to 1.19), indicating that living on the lowest floors (where also all the "exposed" apartments are

Table 3
Truncated age-standardized incidence rates for hematological neoplasms and brain tumors by exposure to extremely low frequency magnetic fields from indoor transformer stations. The European Standard Population (Eurostat, 2012) was used for standardization. Only persons with age ≥18 years were followed up for neoplasm development. The total person-years were 165,240 for the exposed residents and 3,323,413 for the referents.

Neoplasm type	Age-standardized incidence rates (cases per 100,000 person-years)	
	Exposed	Reference
Any hematological neoplasms	26.4	43.1
All types of leukemia	4.69	11.6
Lymphoid leukemia	4.06	5.30
Acute lymphocytic leukemia	1.70	0.84
Chronic lymphocytic leukemia	2.36	4.46
Myeloid leukemia	0.32	5.42
Acute myeloid leukemia	0.32	3.40
Chronic myeloid leukemia	0.00	1.48
Lymphoma	16.1	24.8
Hodgkin lymphoma	0.46	2.74
Non-Hodgkin lymphoma	15.7	22.2
Multiple myeloma	6.38	6.75
Glioma	8.09	5.11
Meningioma	6.35	7.92

Table 4
Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors by exposure to extremely low frequency magnetic fields from indoor transformer stations. The total person-years were 165,240 for the exposed residents and 3,323,413 for the referents.

Neoplasm type	Exposed cases	Referent cases	HR[a] (95% CI)
Any hematological neoplasms	37	1,065	0.75 (0.54–1.03)
All types of leukemia	9	278	0.69 (0.36–1.35)
Lymphoid leukemia	7	128	1.17 (0.55–2.50)
Acute lymphocytic leukemia	4	28	2.86 (1.00–8.15)
Chronic lymphocytic leukemia	3	100	0.65 (0.21–2.05)
Myeloid leukemia	1	133	0.16 (0.02–1.15)
Acute myeloid leukemia	1	87	0.25 (0.03–1.77)
Chronic myeloid leukemia	0	37	0.00 (0.00–1.70)[b]
Lymphoma	20	636	0.67 (0.43–1.05)
Hodgkin lymphoma	1	96	0.20 (0.03–1.45)
Non-Hodgkin lymphoma	19	540	0.76 (0.48–1.20)
Multiple myeloma	9	148	1.33 (0.68–2.61)
Glioma	13	183	1.47 (0.84–2.57)
Meningioma	5	235	0.46 (0.19–1.11)

[a] Adjusted for age and gender.
[b] Conditional maximum likelihood estimate of rate ratio with mid-P exact confidence interval.

located) was not associated with unknown confounding factors (Table 5).

3.3. Exposure gradient (duration of exposure)

The analysis by duration of residence supported increased risk for ALL and glioma but decreased risk for most hematological neoplasms among individuals exposed to residential MFs (Fig. 2; see Table S5 for exact HRs and 95% CIs). The HR for ALL increased to 3.61 (95% CI: 1.05–12.4), when only residence times ≥ 3 years were considered, consistently with the expectation that longer duration of exposure is associated with increased effect size. The reduced risk of any hematological neoplasms was most pronounced for residence times ≥10 years (HR: 0.47; 95% CI: 0.22–0.99), while the HRs for residence times < 3 years and 3 - < 10 years were 0.79 (95% CI: 0.46–1.35) and 0.92 (95% CI: 0.56–1.52), respectively. Similarly, the risk of all leukemia types combined was low for long residence times, with a rate ratio of 0.0 (95% CI: 0–0.69) for residence time ≥ 10 years and HR of 0.85 (95% CI: 0.31–2.30) for residence time 3 - < 10 years. The increasing trend for ALL and the decreasing trends for any hematological neoplasms and all leukemias were statistically significant. The HRs for CLL and lymphoma were also lowest for the longest durations of residence, but there was no statistically significant trend. This analysis was not meaningful for myeloid leukemia, because there was only one exposed case. Concerning brain tumors, the HR for glioma increased with increasing duration of residence. The trend was statistically significant although all 95% CIs included 1.0. In case of meningioma, the apparent effect size did not increase with exposure time: the risk reduction was largest among individuals who had resided in the buildings for <3 years and the HR exceeded 1.0 at the longest duration of residence.

Table 5
Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors among persons who have resided in first or ground floor (FGF) apartments. The total person-years were 877,994 for FGF residents and 3,323,413 for other floor residents.

Neoplasm type	Cases, FGF	Cases, other floors	HR[a] (95% CI)
Any hematological neoplasms	287	1,065	1.06 (0.93–1.21)
All types of leukemia	70	278	0.99 (0.76–1.29)
Lymphoid leukemia	28	128	0.87 (0.58–1.30)
Acute lymphocytic leukemia	6	28	0.82 (0.34–1.99)
Chronic lymphocytic leukemia	22	100	0.88 (0.55–1.40)
Myeloid leukemia	36	133	1.06 (0.73–1.53)
Acute myeloid leukemia	25	87	1.12 (0.72–1.75)
Chronic myeloid leukemia	9	37	0.95 (0.46–1.97)
Lymphoma	184	636	1.14 (0.96–1.34)
Hodgkin lymphoma	30	96	1.08 (0.71–1.64)
Non-Hodgkin lymphoma	154	540	1.13 (0.94–1.35)
Multiple myeloma	33	148	0.90 (0.62–1.31)
Glioma	52	183	1.10 (0.81–1.49)
Meningioma	71	235	1.19 (0.91–1.55)

[a] Adjusted for age and gender.

3.4. Age at start of exposure

Analysis of age at the start of exposure indicated that the risk of adult ALL may be particularly associated with childhood exposure, with HR (based on two cases) of 11.5 (95% CI: 1.92–68.9) for MF exposure during the first 2 years of life (Table 6). Early childhood exposure was associated with high HRs also for all lymphoid leukemia and all leukemia combined, but these were based on ALL alone. However, the increased adult ALL risk may not be totally dependent on childhood exposure, as a suggestive increase of HR (1.86; 95% CI: 0.44–7.89) was observed also for exposures starting at ages of 15 years and above. This type of analysis was not meaningful for myeloid leukemia, as there was only one exposed case. The suggestive MF-related reduction in lymphoma risk seemed to be associated only with exposure later in life (≥15 years after birth), but it should be noted that the very low number of expected cases makes it difficult to observe any risk reduction associated with early exposure. The possible increase in glioma risk also seemed to be associated only with MF exposure at ≥ 15 years of age. However, it is hard to evaluate any differences by age at start of exposure, as the number of cases was very low (even in the reference group) among those who had resided in the study buildings in childhood. Meningioma occurred in the exposed group only among those who had moved into the buildings at the age of 15 years or higher, but the number of cases was low also among those referents who had resided in the study buildings in childhood.

The incidence rate in each group plotted cumulatively across age at the start of residence in the buildings (Fig. 3A) supports the relevance of childhood MF exposure in ALL but the data does not exclude the possibility that exposure at any age may increase the risk of ALL. As the risk of all other leukemias was tentatively decreased by MF exposure, the data of all leukemia but ALL were combined in this visualization. The resulting graph (Fig. 3B) suggests almost total depletion of new cases of most leukemia types (other than ALL) among those who have moved into the apartments next to transformer stations at the age of 30 or above. The graph for lymphoma (Fig. 3C) also suggests reduction in the proportion of cases among those who have moved into the "exposed apartments" at the age of 40 or above. The effect (if there is any) on glioma seems to be rather independent of age at the onset of exposure (Fig. 3D). The possible reduced risk of meningioma appears to be associated with MF exposure starting at any age (Fig. 3E).

4. Discussion

This study was designed to investigate possible increased risks of hematological malignancies and brain tumors in adults exposed to residential ELF MFs. The results of this study lend limited support to the hypothesis that ELF MFs affect the biology of hematological neoplasms. However, rather than a general increase in cancer risk, the data suggest differential effects depending on type of neoplasm: while an elevated HR was suggested for ALL (based on four exposed cases), the risk of most other hematological neoplasms seemed to be decreased by residential ELF MF exposure. The findings should be interpreted cautiously, as all 95% CIs of the HRs included 1.00 in the analysis that included all exposures ≥1 month. However, some effect directions observed in the main analysis were consistently supported by the results of the analysis evaluating exposure gradient (dependence of HR on duration of residence), suggesting enhancing effects on ALL and glioma and protective effects on overall hematological neoplasms, particularly leukemia.

The analysis focusing on age at start of exposure was based on very low numbers; the results are presented here only as hypothesis-generating findings that may be of interest for possible further studies. Also these results were consistent with differential effects on ALL and other hematological neoplasms: ALL appeared to be associated with childhood exposure to ELF MFs, while the incidence of other leukemia (and lymphoma to a lesser extent) showed an inverse association with exposure during adult life.

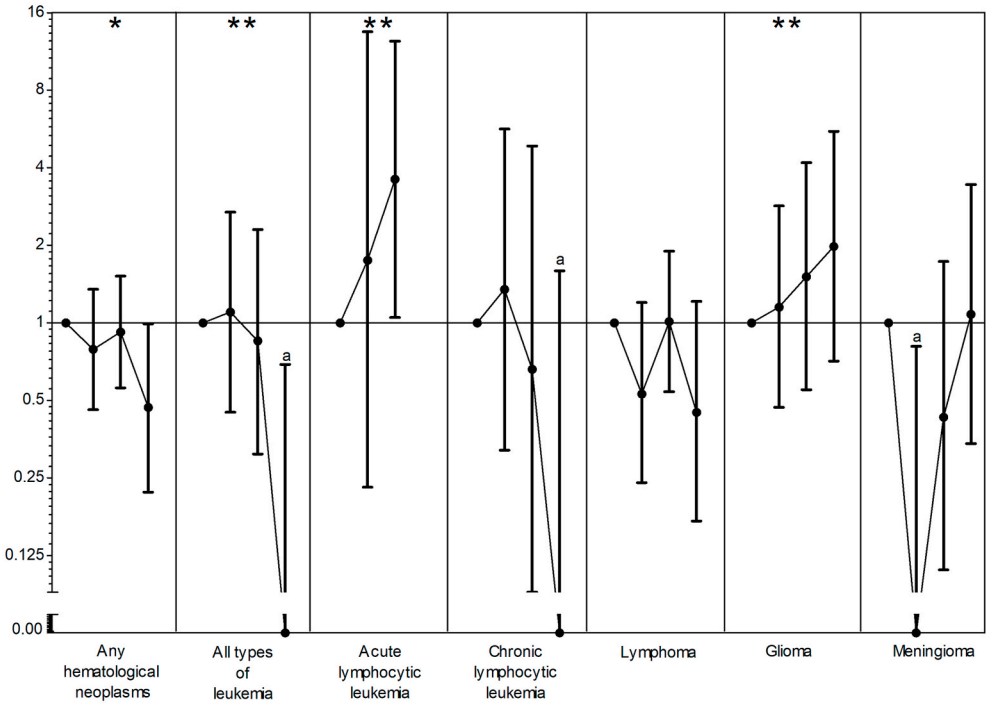

Fig. 2. Exposure gradient analysis: Adjusted hazard ratios (95% confidence intervals) for selected hematological neoplasms and brain tumors by duration of exposure to extremely low frequency magnetic fields from indoor transformer stations. For each type of neoplasm, the exposure durations from left to right are reference, < 3 years, 3 - <10 years and ≥10 years. The highest exposure category considered for acute lymphocytic leukemia was ≥3 years, because there were no cases exposed for ≥10 years and the number of expected cases was also very low (~0.3). [a] No observed case in the exposed group. Conditional maximum likelihood estimate of rate ratio with mid-P confidence interval is shown; **P for trend <0.01; *P for trend <0.05.

Table 6
Hazard ratios (HR) and 95% confidence intervals (95% CIs) for hematological neoplasms and brain tumors by age at start of exposure to extremely low frequency magnetic fields (referents: age at start of residence).

Age at start of exposure	Exposed cases	Referent cases	HR[a] (95% CI)
Any hematological neoplasm			
<2 years	2	17	1.86 (0.43–8.08)
2 - <15 years	2	39	0.74 (0.18–3.07)
≥15 years	33	1,009	0.71 (0.50–1.01)
All types of leukemia			
<2 years	2	4	8.70 (1.59–47.6)
2 - <15 years	0	7	0.00 (0.00–7.57)[b]
≥15 years	7	267	0.57 (0.27–1.21)
Lymphoid leukemia			
<2 years	2	3	11.5 (1.92–68.9)
2 - <15 years	0	3	0.00 (0.00–24.3)[b]
≥15 years	5	122	0.89 (0.36–2.17)
Acute lymphocytic leukemia			
<2 years	2	3	11.5 (1.92–68.9)
2 - <15 years	0	2	0.00 (0.00–49.2)[b]
≥15 years	2	23	1.86 (0.44–7.89)
Lymphoma			
<2 years	0	12	0.00 (0.00–4.48)[b]
2 - <15 years	2	31	0.94 (0.23–3.91)
≥15 years	18	593	0.66 (0.41–1.05)
Glioma			
<2 years	0	3	0.00 (0.00–27.1)[b]
2 - <15 years	1	13	1.08 (0.14–8.28)
≥15 years	12	167	1.53 (0.85–2.75)
Meningioma			
<2 years	0	3	0.00 (0.00–27.1)[b]
2 - <15 years	0	8	0.00 (0.00–6.44)[b]
≥15 years	5	224	0.49 (0.20–1.19)

[a] Adjusted for age and gender.
[b] Conditional maximum likelihood estimate of rate ratio with mid-P confidence interval is shown.

Suggestive effects on the risk of neoplasms were seen only in apartments classified in the high exposure category. In a sample of 30 residential buildings in three Finnish cities (Ilonen et al., 2008), exposure to fields above 0.4 μT was common in such residences (the whole-apartment 24-h average was ≥0.4 μT in 63% of apartments). No effects were found in other ground or first floor residences, in which the magnetic flux density is somewhat higher than in the reference apartments (see Table S1), but 0.4 μT is less common (24-h average ≥ 0.4 in 14% of residences) than in the high exposure category apartments. Assuming that this sample of 30 buildings is representative of Finnish buildings with indoor transformer stations, our results are consistent with the childhood leukemia studies suggesting increased risk when flux density is 0.4 μT or higher but showing little evidence of effects at lower flux densities (Ahlbom et al., 2000).

This study had several strengths. Assessing ELF MF exposure solely based on apartment location (without contacting the residents) enabled elimination of selection bias. This approach to exposure assessment has been validated in several studies. In the study by Ilonen et al. (2008), the specificity of exposure classification with the 0.4 μT cutoff point was 0.97. This was a limited sample of 30 buildings in three Finnish cities, but measurements performed in other countries (Hareuveny et al., 2011; Huss et al., 2013; Kandel et al., 2013; Röösli et al., 2011; Thuroczy et al., 2008; Yitzhak et al., 2012; Zaryabova et al., 2013) support the conclusion that residents of apartments above transformer stations are exposed to ELF MFs that are clearly higher than the average residential background level. A further advantage of the study was that outcome data was obtained from a reliable nationwide register with high completeness of registration. We were also able to follow the cohort members for long periods of time.

In comparison to studies based on residences near powerlines, the advantage of our approach is that exposure levels exceeding 0.4 or 0.2 μT are common in apartments next to transformer stations. Interestingly, a recent study on childhood leukemia in relation to distance from power lines and calculated MFs provided evidence that increased risk was associated with MFs ≥0.4 μT only very close to high voltage (>200 kV) power lines, not with similar field intensities produced solely by lower voltage lines (Crespi et al., 2019). This finding argues against MFs as the sole explanation for the increased risks observed close to power lines and suggests the involvement of other factors linked to power lines. Studies addressing high MF exposure from other sources, such as transformer stations, are therefore valuable for evaluating the possible causal role of ELF MFs.

A disadvantage resulting from our approach was that we had no

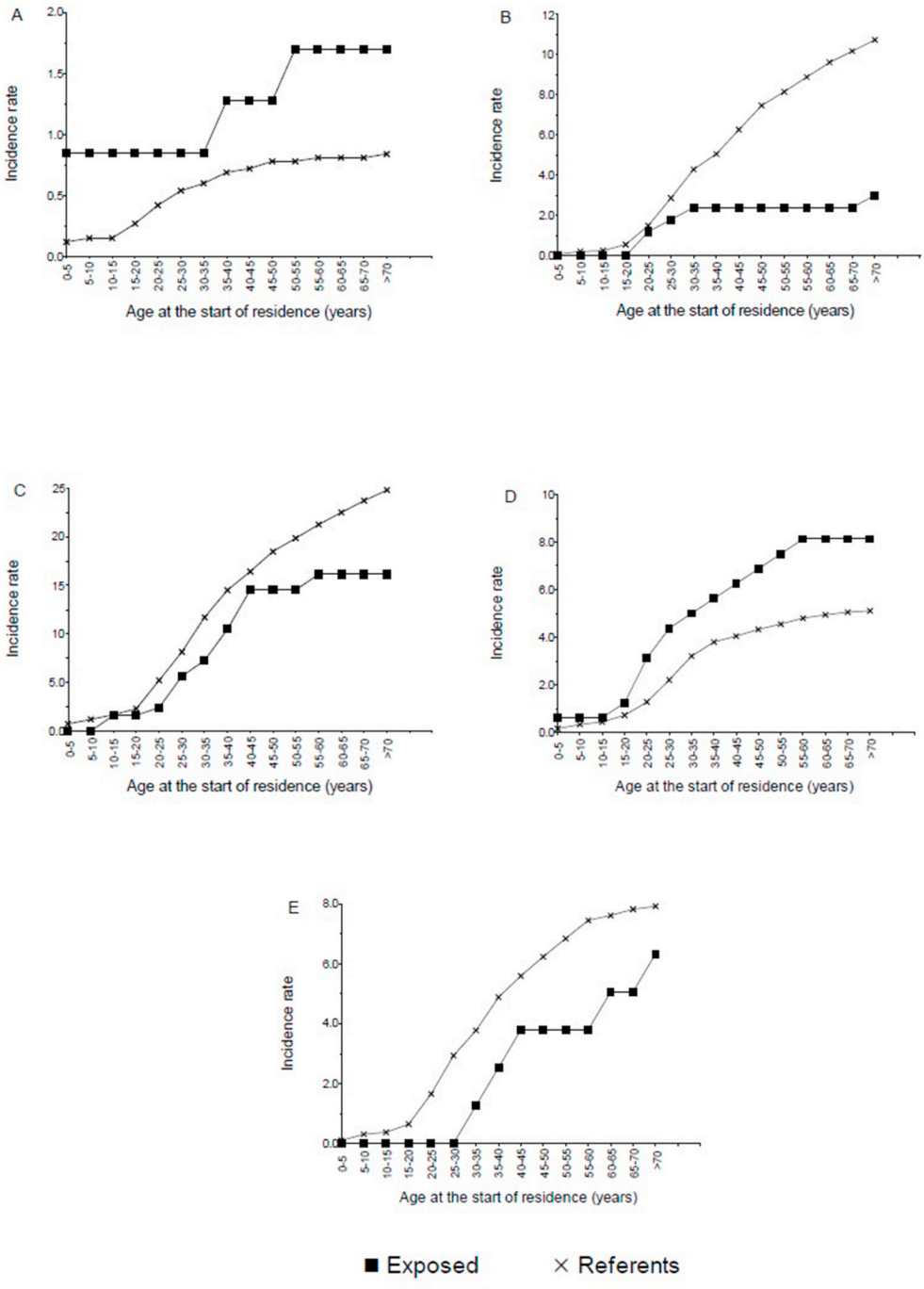

Fig. 3. Impact of age at start of exposure on the risk of neoplasms: contribution of the number of cases observed in each 5-year class to the final age-standardized incidence rate (per 100,000 person-years). Apparent incidence rate (taking into account only persons with the specified age at start of residence) is plotted cumulatively as a function of age at start of residence. The European Standard Population (Eurostat, 2012) was used for standardization. (A) acute lymphocytic leukemia; (B) all leukemia excluding acute lymphocytic leukemia; (C) lymphoma; (D) glioma; (E) meningioma.

information about exposure to ELF MFs sources other than transformer stations. Other residential sources are not likely to be important, as the transformer stations are dominating sources in the apartments that were classified as "exposed", and clearly elevated levels are rare in other apartments of the buildings (Ilonen et al., 2008). Some members of the cohort may have experienced relatively high occupational exposures. However, there is no reason to assume that the distribution of occupations, and hence occupational ELF MF exposure, would differ between persons living next to a transformer stations and the rest of the cohort.

As the study subjects were not contacted, information about personal confounding factors such as smoking was not available. This limitation was at least partly overcome by the study design; selecting both exposed and referent individuals from the same buildings minimized differences in potential environmental confounders (e.g., air pollution), but it also favored similar distributions of all potential confounding factors including lifestyle-related factors, which are associated with socioeconomic status. Some remining confounding might be associated with living at the lowest floors of the buildings (where also all "exposed" apartments are), as apartment prices are slightly higher at higher floors (possibly causing differences in social status) and living near the ground level may affect the level of some environmental agents, such as radon (Valmari et al., 2012). The data allowed testing this possibility by assessing cancer risk among such first or ground floor residents who did not live next to a transformer station. This analysis did not provide any evidence of such confounding that would explain the suggested increased and decreased risks among the exposed residents. Another limitation of the study was low number of cases, which was evident especially when different cancer subtypes were studied individually or

when analyzing the effect of age at the start of exposure. This led to broad confidence intervals in many analyses.

Estimation of MF exposure levels in apartment above transformer stations is possible, if information about structural characteristics of the transformers is available (Okokon et al., 2014). Unfortunately, it was not possible to get such data from the electricity distribution companies. As a result, we could not study dose response in relation to magnetic flux density. However, given the limited understanding of what comprises the MF "dose" (Auvinen et al., 2000; Eskelinen et al., 2003; Juutilainen et al., 1996), time-average magnetic flux density may not be the most pertinent exposure metric for predicting possible biological effects. In the present study, duration of residence in an "exposed" apartment (as a proxy for the duration of residential exposure to an elevated MF) was used in the exposure gradient analysis; duration of exposure may be the most relevant exposure metric, if the exposure-response relationship has a threshold and a plateau above the threshold (Eskelinen et al., 2002).

While many previous studies have investigated adult leukemia and brain tumors in relation to occupational ELF MF exposure (Huss et al., 2018; Kheifets et al., 2008b) only a few studies have addressed possible risks associated with residential exposure. Some past studies have reported increase or no risks associated with distance to power lines (Coleman et al., 1989; Baldi et al., 2011; Lowenthal et al., 2007; McDowall, 1986), but the most interesting ones are those that have assessed ELF MF exposure using more reliable methods such as MF measurements or model calculations to determine MFs caused by nearby power lines. Many of such studies on leukemia have reported either no risk increase (Verkasalo, 1996) or risk estimates above 1.0 but wide confidence intervals for MF exposures above cutoffs of 0.2 or 0.3 μT (Feychting et al., 1997; Li et al., 1997; Tynes and Haldorsen, 2003). As our study suggests differential effects on different types of leukemia, the results are not necessarily inconsistent with studies on overall leukemia suggesting no or weak effects. Unfortunately, only a few studies included separate analyses for different types of leukemia/hematological neoplasms. The study by Li et al. (1997) showed some consistency with our results. The risk of ALL was highest with an OR of 1.7 (95% CI: 1.0–3.1), while smaller risk estimates were reported for CLL (0.6; 95% CI: 0.1–2.6), AML (1.1; 95% CI: 0.7–1.7) and CML (1.5; 95% CI: 0.9–2.6). Verkasalo (1996) reported that the overall risk of leukemia associated with cumulative MF exposure $\geq$ 2 μT-years was below unity (SIR: 0.7; 95% CI: 0.19–1.81), while the risk estimate for CLL was 1.46 (95% CI: 0.30–4.26). The number of ALL and AML cases was low, and there were no cases exposed at $\geq$ 2 μT-years. The SIR for ALL in the 1.00–1.99 μT-year exposure category was 2.38 (95% CI: 0.06–13.3), based on one exposed case. The SIR for other leukemia associated with exposure $\geq$2 μT-years was 0.65 (95% CI: 0.02–3.59) (Verkasalo, 1996). Tynes and Haldorsen (2003) reported an OR of 1.5 (95% CI: 0.8–3.0) for all leukemia associated with exposure to MFs $\geq$0.2 μT. The risk estimate for CLL was highest with an OR of 2.8 (95% CI: 0.7–10.7), while the ORs for ALL and AML were 1.7 (95% CI: 0.2–13.3) and 1.6 (95% CI: 0.4–1.0), respectively. Feychting et al. (1997) reported a RR of 1.3 (95% CI: 0.8–2.2) for all leukemia associated with exposures $\geq$0.2 μT. The risk estimate for AML was the highest with a RR of 2.4 (95% CI: 0.9–5.7), while the RRs for CML and CLL were 2.1 (95% CI: 0.8–5.5) and 0.8 (95% CI: 0.3–1.8) respectively. Overall, other studies do not consistently support our findings suggesting increased risk of ALL but decreased risks of other leukemias. However, the highest exposure groups are small and the highest exposure levels low in all studies that have addressed leukemia and lymphoma subtypes in residences near power lines, and the confidence intervals are wide.

In the present study, the HR for glioma was above 1.00 and showed statistically significant increase with increasing exposure. However, the confidence intervals were wide. This result alone does not provide clear evidence for malignant brain tumor risk associated with ELF MF exposure, but it is not inconsistent with studies reporting increased risks associated with occupational exposure (Huss et al., 2018; Kheifets et al., 2008b). The below-unity HR for meningioma is in contrast with the studies reporting increased risks associated with occupational ELF MF exposure (Huss et al., 2018; Kheifets et al., 2008b). The results of previous studies on brain tumors in relation to residential exposure are inconsistent (Baldi et al., 2011; Elliot et al., 2013; Li et al., 1997), and some of them have not made a difference between glioma and other brain tumors (Elliot et al., 2013; Verkasalo et al., 1996). Interestingly, Li et al. (2003) reported that the average age at brain tumor diagnosis was higher among individuals whose estimated residential ELF MF exposure level was $\geq$0.2 μT than among those whose exposure was below this cutoff. This delay in diagnosis was observed only in "unclassified or other" brain tumors, not in glioma, consistent with inhibited development of meningioma.

There is no generally accepted biophysical mechanism that could explain carcinogenic effects of low-level ELF MFs (IARC, 2002; WHO, 2007). One of the most plausible mechanisms involves radical pairs as intermediates of chemical reactions. This radical pair mechanism (RPM) seems to be involved in the avian magnetic compass sense (Hore and Mouritsen, 2016), and it could therefore potentially explain also other effects of weak MFs. We have proposed a hypothesis for explaining how the primary biophysical interaction (i.e. RPM) could lead to cancer-relevant biological effects through dysregulation of the circadian system and DNA damage responses (Juutilainen et al., 2018). A related alternative hypothesis was proposed by Vanderstraeten et al. (2012). However, it remains a major challenge to explain how a 0.4 μT oscillating MF could induce carcinogenic effects in the presence of the much stronger (~50 μT) static MF of the earth (Hore , 2019; Juutilainen et al., 2018).

Apart from explaining increased risk of ALL, the putative mechanism would need to explain decreased risk of other hematological malignancies. Disruption of the circadian clock is believed to enhance the development of cancers, including leukemia and lymphoma (Rana et al., 2014; Yang et al., 2006; Zhu and Zheng, 2008). The hypothesized MF-induced disruption of the circadian clock would thus explain only increased risks. However, there is limited evidence from two studies that dysfunction of certain circadian genes might be associated with anti-leukemic effects in AML (Puram et al., 2016) and CLL but not ALL (Hanoun et al., 2012). These findings might be related to our observations suggesting inhibited development of AML and CML in adults who move into the apartments above transformer stations.

The results of previous studies on occupational MF exposure are consistent with a possible small increase in the risk of leukemia, the evidence being stronger for myeloid leukemia than for lymphoid leukemia (Huss et al., 2018; Kheifets et al., 2008b). If both the increased myeloid leukemia risk associated with occupational exposure and the reduced risk suggested by this study are assumed to be true effects, what could explain the opposite effects? The most obvious difference between occupational and residential MF exposure is the diurnal rhythm of exposure - residential exposure occurs at night, while (in most cases) occupational exposure occurs during the day. However, there is little evidence of different effects from daytime vs. nighttime exposure to MFs. A pooled analysis was carried out to evaluate the hypothesis that nighttime ELF MF exposure is more relevant to childhood leukemia than 24-h exposure (Schüz et al., 2007). No essential differences were seen between nighttime and 24-/48-h exposures, and the slope of the exposure-response trend was actually slightly steeper for 24-/48-h exposure than for nighttime exposure.

If the diurnal timing of MF exposure modifies biological responses, it is worth noting that the diurnal pattern of childhood exposure due to transformer stations differs from that of adults. Due to variation in power consumption (high during daytime) small children (those who do not go to school or kindergarten) experience higher exposure during day than at night, i.e., the diurnal variation in their exposure resembles that of occupationally exposed adults. Exposure from power lines follows a similar diurnal variation. It remains to be investigated whether the high day-time exposure plays any role in our observation that adult ALL risk may be associated particularly with childhood exposure, and in the

previous findings showing a link between powerline MFs and childhood leukemia (which is mainly ALL).

The suggested inhibition of certain tumor types (particularly other leukemia than ALL) was an unexpected and unique finding. As discussed above, previous epidemiological studies provide little support for such anticarcinogenic effects, but their value as negative evidence is limited due to the lack of subjects exposed to MFs ≥0.4 μT. Although most animal experiments designed to test carcinogenic effects of ELF MFs have found no effects (Juutilainen et al., 2000), two studies reported slight (non-significant or marginally significant) reduction of radiation-induced lymphoma in mice exposed to MFs (Babbit et al., 2000; Heikkinen et al., 2001), while a third study with a different study design (small radiation dose, MF exposure started prenatally) reported increased incidence of lymphoma/leukemia (Soffritti et al., 2016).

5. Conclusions

The results lend limited support to the hypothesis that ELF MFs ≥0.4 μT influence the biology of hematopoietic and lymphoid tissue neoplasms. However, only the risk of ALL was increased among the cohort members exposed to MFs. This finding, suggesting an association between adult ALL and childhood MF exposure, was based on small number of exposed ALL cases. The risk of most other hematological malignancies was decreased, in contrast to many previous epidemiological studies. The slightly increased HR for glioma does not alone provide clear evidence for malignant brain tumor risk associated with ELF MF exposure, but it is not inconsistent with increased risks reported in previous studies. There was weak evidence that the risk of meningioma might be reduced rather than increased by MF exposure. The suggested differential effects on different types of neoplasms call for additional studies that could shed light on the mechanisms and overall public health impact of ELF MF exposure.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2021.113712.

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