RESEARCH ARTICLE

Exposure to extremely low-frequency magnetic fields and childhood cancer: A systematic review and meta-analysis

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Abstract

Background

Extremely low frequency magnetic fields (ELF-MFs) are classified as a possible carcinogenic factor (Group 2B). This study assessed the association between ELF-MFs and childhood cancer through a systematic review and meta-analysis.

Methods

Three databases were searched in January 2020. We conducted a meta-analysis for the association between the ELF-MFs exposure level and childhood cancer.

Results

A total of 33 studies were identified. Thirty studies with 186,223 participants were included in the meta-analysis. Children exposed to 0.2-, 0.3-, and 0.4-μT ELF-MFs had a 1.26 (95% confidence interval [CI] 1.06–1.49), 1.22 (95% CI 0.93–1.61), and 1.72 (95% CI 1.25–2.35) times higher odds of childhood leukemia. In childhood brain tumors, children exposed to 0.2-μT had a 0.95 (95% CI 0.59–1.56) times higher odds, and those exposed to 0.4-μT ELF-MFs had a 1.25 (95% CI 1.25–2.35) times higher odds. Children exposed to 0.2- and 0.4-μT ELF-MFs had a 1.10 (95% CI 0.70–1.75) and 2.01 (95% CI 0.89–4.52) times higher odds of any childhood cancers.

Conclusions

Significant associations were observed between exposure to ELF-MFs and childhood leukemia. Furthermore, a possible dose-response effect was also observed.
Introduction

The debate on the effect of electromagnetic fields (EMFs) on the human body still continues, and several studies have investigated the effect of magnetic fields that are not well shielded by objects [1–3]. The question of whether exposure to extremely low-frequency magnetic fields (ELF-MFs) from power transmission and distribution or the use of electrical appliances is associated with an increased risk of childhood cancer has engendered scientific debate [4–6]. In 2001, the ELF-MFs were classified by the International Agency for Research on Cancer (IARC) as possibly carcinogenic (Group 2B), based on the limited clinical evidence, inadequate experimental support, and the lack of plausible mechanisms at the exposure levels that were observed in epidemiological studies [7, 8]. This classification was endorsed by the subsequent weight of evidence assessments carried out by the World Health Organization (WHO) [8]. Subsequently, clinical evidence emerged from epidemiological studies on the etiology of childhood leukemia that indicated a weak association with ELF-MFs [9–12].

The WHO International Advisory Committee presented a Research Agenda for ELF-MFs whereby they indicated that epidemiological studies are of primary importance in health risk assessment, and that high-priority research needs to conduct pooled analyses of existing childhood cancer studies [13]. Until 2010, several pooled analyses of ELF-MFs and childhood leukemia and brain tumor were conducted [4, 5, 14]. However, these studies have not conducted in accordance with the methodology of systematic review and meta-analysis. They were also pooled analyses based on only 10 studies of ELF-MFs exposure and childhood brain tumors [4], and nine and seven studies on ELF-MFs and childhood leukemia [5, 14]. Additionally, 12 studies have been conducted since those analyzes [12, 15–25]. Therefore, the pooled analyses need to be updated with the results from recent studies.

The first epidemiological study of the association between the exposure to ELF-MFs and childhood cancer was published in 1979 [26]. Over the past four decades, the potential health effects of exposure to ELF-MFs have been extensively investigated in epidemiological studies. Nonetheless, no systematic reviews and meta-analysis of the association between exposure to ELF-MFs and childhood cancer has been undertaken. Therefore, a systematic review is crucial for the scientific verification of the ELF-MFs association with cancer.

Therefore, it is necessary to comprehensively search and review the literature with an appropriate methodology, and to carry out a meta-analysis to confirm the association between exposure to ELF-MFs and childhood cancer.

Aim

We aimed to assess the association between ELF-MFs and childhood cancer through a systematic review and meta-analysis of relevant studies.

Design

The procedure adopted in this study followed the guidelines of the Cochrane Collaboration [27]. Moreover, the results are reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [28].

Methods

Systematic search

Using the search strategy recommended by Cochrane [29], the search terms were chosen to obtain highly sensitive results: the keywords “electromagnetic field,” “child,” “adolescent,” and “epidemiologic studies” were combined with the Medical Subject Headings and Emtree terms
S1 Table. We searched in the international databases of MEDLINE (1946 to January Week 3 2020), EMBASE (1988 to January Week 3 2020), and Web of Science (1995 to January Week 4 2020). Moreover, the reference lists of the retrieved studies were reviewed to identify additional studies that were suitable for inclusion. Literature searching has been performed by the first author who is an expert of the task with trained experiences. Our search strategy has also been confirmed by a qualified librarian.

Study selection

Studies were searched, reviewed, and selected by two authors independently (J. P. and G. S.), using predefined criteria. Full texts for studies that met the inclusion criteria were identified and reviewed. In cases where no consensus could be reached, the issue was resolved through either further discussion or a separate examination by another author (J.L.), who is a statistical expert. However, there were no notable inconsistencies with the initial selection.

The inclusion criteria were: (1) epidemiologic studies (cohort or case-control design); (2) studies on exposure of ELF-MF; (3) studies with childhood cancer; (4) studies indicating subject number by each group exposure level; (5) based on magnetic field measurements or the calculated field; and (6) the article written in English. Abstracts presented at congresses, reviews, letters, editorials, and unpublished data were excluded.

Quality appraisal

The Newcastle–Ottawa Scale (NOS) was used to determine the risk of bias in the studies that were included [30] in the systematic review. The NOS, a star system that allows a semi-quantitative assessment of nonrandomized study quality, contained eight items that were categorized into three major components, including selection, comparability, and exposure (case-control studies) or outcome (cohort studies). The scale ranges from zero to nine stars, where the latter represents the highest methodological quality. Two authors (J.P. and G.S.) independently assessed each study, discussed any discrepancies, and reached a consensus for all domains. In case of disagreement, the other author resolved the issue.

Data extraction

J.P. and G.S. independently extracted the relevant data from each study, and discussed and resolved any issues that emerged. The data that were abstracted included information on: the first author, publication year, study design, country of origin, eligible population size, study population characteristics, registry group, exposure measurement, and matching variables.

Data synthesis and analysis

We analyzed the data by using Review Manager (version 5.3) for the association between exposure to EMF and childhood cancer. Meta-analyses of the risk of childhood cancer outcomes were conducted to obtain pooled odds ratios (ORs) with the 95% confidence intervals (CIs) in a random effects model in case-control studies. The cohort studies were excluded in meta-analysis due to its differences in EMF exposure levels and outcome variables between studies. The heterogeneity among studies was estimated by using the $I^2$ statistic [31, 32] as well as by the Q test. For the Q test, a $p$-value of less than 0.1 was used as an indicator of the presence of heterogeneity, the $I^2$ statistic provides a measure for quantifying the heterogeneity with regard to the proportion of between-study variation based on the total variation in the estimates. In this study, an $I^2$ value of greater than 50% was considered to denote the existence of substantial heterogeneity among the study results. We conducted analyses that were stratified by the level
of exposure of EMF, and further evaluated the dose–response effect of EMF exposure. Moreover, the sensitivity analysis was performed by individually excluding each study to assess its influence of each study on the overall result of the meta-analysis.

The publication bias was examined graphically by using a funnel plot of a study’s effect size against the standard error. A two-tailed $p$-value of less than 0.05 was considered to be statistically significant.

**Results**

**Search outcomes**

Our systematic search found a total of 3,933 studies. After removing duplicate articles, a total of 3,250 studies were excluded for lack of eligibility for study inclusion on a review of the study title and abstract. A full-text review of the remaining 186 studies was undertaken, and a further 153 studies were excluded. Finally, 33 studies were included in the systematic review for the association of ELF-MFs and childhood cancer [9, 10, 12, 15, 18, 20, 22, 23, 33–56], and 30 studies with 186,223 were included in the meta-analysis. The selection process is summarized in Fig 1.

**Study characteristics**

Table 1 presents the data extracted from all 33 studies. There were 30 case–control studies, and all except one [21] were matched case–control studies. The other three studies had a cohort design [38, 50, 57]. Published between 1988 and 2019 worldwide, all of the studies had a primary research question that was focused on the association between the exposure to ELF-MFs and childhood cancer. The age of the participants in the study population ranged from 1 day to 19 years. In 12 of the included studies, the relationship between ELF-MFs exposures with regard to any childhood cancer was researched. The cancers included lymphoma, brain tumor, and other types of cancers. With regard to the other studies, 18 articles were focused only on childhood leukemia, and some of the research was exclusively directed toward brain tumors.

The included three cohort studies were unable to perform meta-analysis due to differences in exposure levels and outcomes between studies. In a cohort study investigating the risk of cancer in children living close to overhead power lines with a magnetic field of 0.01-μT, the standardized incidence ratio was 0.97 (95% confidence interval [CI], 0.8-1.1), with no statistically significant increases in all cancers [38]. Two of the three cohort studies examined the association between ELF-MFs exposure and survival after diagnosis of childhood leukemia [50, 57]. The results were a survival risk (Hazard Ratio, HR) of 1.9 (95% CI, 0.8–4.9) at 0.3–μT [57] and 3.0 (95% CI, 0.9–9.8) at 0.2–μT [50].

The study characteristics included the year of diagnosis and the registry group (Table 1). The methods for the EMFs exposure assessments are presented from long-term measurements, spot measurements, and the calculated field. For 12 studies, the EMF exposure was calculated and presented through a measurement of the distance to the high-voltage line. In the included case–control studies, the cases and controls were matched by the sex, age, and geographic areas, and the confounding factors were adjusted. In five studies [10, 35, 37, 41, 58], although they did not match with the geographic area variables, we attempted to control for the factors that influenced the outcome, such as selecting a control group from each of the study’s registries.

The absolute numbers of childhood cancer cases and controls for the exposure level of the ELF-MFs were presented in Table 2 along with the OR and 95% CI. The level of exposure to ELF-MFs were predominantly 0.2, 0.3, and 0.4–μT, and the results that were derived from most of the studies were compared with 0.1–μT or less exposure.
Risk of bias assessment

The risk of bias in the studies was evaluated by the NOS for all 30 articles included in the meta-analysis. A total of 30 articles that met all of the selection criteria were assessed for their
| Study                | Subjects                  | Exposure measurement | Matching variables |
|---------------------|---------------------------|----------------------|--------------------|
| Author              | Study design              | Cases  | Controls  | Age          | Diagnosis               | Year of diagnosis | Registry                              | Long-term measurement | Spot measurement | Calculated fields | Sex | Age | Geographic area |
| Savitz et al. 1988  | Matched case-control study | 128    | 207       | 0–14 years   | Any childhood cancer | 1976–1983          | the Colorado Central Cancer Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Myers et al. 1990   | Matched case-control study | 374    | 588       | 0–14 years   | Any childhood cancer | 1970–1979          | the Yorkshire Childhood Cancer Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| London et al. 1991  | Matched case-control study | 162    | 143       | 0–10 years   | Childhood leukemia  | 1980–1987          | the Los Angeles County Cancer Surveillance Program | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Feychting and Ahlbom 1993 | Matched case-control study | 142    | 558       | 0–15 years   | Any childhood cancer | 1960–1985          | the Swedish Cancer Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Olsen et al. 1993   | Matched case-control study | 1,707  | 4,788     | 0–15 years   | Any childhood cancer | 1968–1986          | The nationwide cancer registration system | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Verkasalo et al. 1993a | Cohort study             | 29     | 1027      | 0–19 years   | Any childhood cancer | 1970–1989          |                                  | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Preston-Martin et al. 1996 | Matched case-control study | 437    | 433       | 0–19 years   | Childhood brain tumor | 1984–1991          | the Los Angeles portion of a multicenter | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Linet et al. 1997   | Matched case-control study | 629    | 619       | 0–14 years   | Childhood lymphocytic leukemia | 1989–1994          | the Children’s Cancer Group | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Michaelis et al. 1997 | Matched case-control study | 176    | 414       | 0–14 years   | Any childhood cancer | 1991–1994          | the German Childhood Cancer Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Tynes et al. 1997   | Matched case-control study | 532    | 2,112     | 0–14 years   | Any childhood cancer | 1965–1989          | the Cancer Registry of Norway | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Dockerty et al. 1998 | Matched case-control study | 303    | 303       | 0–14 years   | Childhood leukemia, brain tumor, other solid cancers | 1990–1993          | the New Zealand Cancer Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Green et al. 1999   | Matched case-control study | 189    | 381       | 0–14 years   | Childhood leukemia | 1985–1993          | the Pediatric Oncology Group Registry | ✓                     | ✓                | ✓                | ✓               | ✓               |
| Study | Subjects | Exposure measurement | Matching variables |
|-------|----------|----------------------|--------------------|
| McBride et al. | 1999 Canada Matched case-control study | Cases 399 Controls 399 Age 0–10 years Diagnosis Childhood lymphatic leukemia Year of diagnosis 1990–1995 Registry In British Colombia and Quebec | ✓ | ✓ | ✓ | ✓ |
| UKCCS investigators | 1999 UK Matched case-control study | Cases 2226 Controls 2226 Age 0–14 years Diagnosis Any childhood cancer Year of diagnosis 1991–1996 Registry the UKCCS | ✓ | ✓ | ✓ | ✓ |
| Kleinerman et al. | 2000 USA Matched case-control study | Cases 408 Controls 408 Age 0–14 years Diagnosis Childhood lymphoblastic leukemia Year of diagnosis 1989–1993 Registry the Children’s Cancer Group | ✓ | ✓ | ✓ | ✓ |
| Bianchi et al. | 2000 Italy Matched case-control study | Cases 101 Controls 412 Age 0–14 years Diagnosis Childhood leukemia Year of diagnosis 1976–1992 Registry the National Electricity Board | ✓ | ✓ | ✓ | ✓ |
| Schü z et al. | 2001 Germany Matched case-control study | Cases 514 Controls 1,301 Age 0–14 years Diagnosis Childhood leukemia Year of diagnosis 1992–1994 Registry the German Childhood Cancer Registry (GCCR) | ✓ | ✓ | ✓ | ✓ |
| Foliart et al. | 2006 USA cohort study | Cases 1–15 years Diagnosis Childhood lymphoblastic leukemia Year of diagnosis 1996–2004 Registry the Pediatric Oncology Group (POG) | ✓ | ✓ | ✓ | ✓ |
| Kabuto et al. | 2006 Japan Matched case-control study | Cases 312 Controls 603 Age 0–15 years Diagnosis Childhood leukemia Year of diagnosis 1999–2001 Registry the 5 major children’s cancer study groups in Japan | ✓ | ✓ | ✓ | ✓ |
| Feizi and Arabi | 2007 Iran, Tabriz Matched case-control study | Cases 0–14 years Diagnosis Childhood leukemia Year of diagnosis 1998–2004 Registry the Children’s Hospital of Tabriz | ✓ | ✓ | ✓ | ✓ |
| Svendsen et al. | 2007 Germany cohort study | Cases 1–14 years Diagnosis Childhood lymphoblastic leukemia Year of diagnosis 1988–1994 Registry | ✓ | ✓ | ✓ | ✓ |
| Kroll et al. | 2010 UK Matched case-control study | Cases 9695 Controls 9695 Age 0–14 years Diagnosis Any childhood cancer Year of diagnosis 1962–1995 Registry the National Registry of Childhood Tumours | ✓ | ✓ | ✓ | ✓ |
| Malagoli et al. | 2010 Italy Matched case-control study | Cases 46 Controls 184 Age 0–13 years Diagnosis Childhood leukemia Year of diagnosis 1986–2007 Registry the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) | ✓ | ✓ | ✓ | ✓ |

(Continued)
| Study | Author Year | Country | Study design | Cases | Controls | Age | Diagnosis | Year of diagnosis | Registry | Exposure measurement | Matching variables | Calculated fields |
|-------|-------------|---------|--------------|-------|----------|-----|-----------|-------------------|----------|----------------------|------------------|------------------|
|       | Saito et al. 2010 | Japan | Matched case-control study | 55 | 99 | 0-14 | Childhood brain tumor | 1999-2002 | network of 107 hospitals | √ | √ | √ |
|       | Does et al. 2011 | USA | Matched case-control study | 0-8 | 0-18 | Childhood lymphocytic leukemia | 2002-2007 | Eight hospitals in the State of Sao Paulo | √ | √ | √ |
|       | Wuensch Filho et al. 2011 | Brazil | Matched case-control study | 162 | 565 | 0-18 | Childhood leukemia | 2003-2009 | the National Cancer Institute (NCI) | √ | √ | √ |
|       | Jirik et al. 2012 | Czech Republic | Matched case-control study | 79 | 79 | 0-14 | Childhood leukemia | 2001-2007 | | √ | √ | √ |
|       | Ba Hakim et al. 2014 | Malaysia | Matched case-control study | 108 | 118 | 0-14 | Childhood leukemia | 2003-2012 | | √ | √ | √ |
|       | Bunch et al. 2015 | UK | Matched case-control study | 52,525 | 52,525 | 0-14 | Childhood leukemia | 1986-2008 | the Danish Registry of Childhood Tumours (NRCT) | √ | √ | √ |
|       | Pedersen et al. 2015 | Denmark | Matched case-control study | 3,277 | 9,129 | 0-14 | Childhood leukemia | 1986-2008 | the Danish Data Protection Agency | √ | √ | √ |
|       | Salan et al. 2015 | Italy | Matched case-control study | 412 | 567 | 0-10 | Childhood leukemia | 1986-2008 | | √ | √ | √ |
|       | Khedr et al. 2017 | USA | Matched case-control study | 5,788 | 5,788 | 0-15 | Childhood leukemia | 1986-2008 | the California Cancer Registry | √ | √ | √ |
|       | Greep et al. 2019 | USA | Matched case-control study | 4,879 | 4,835 | 0-14 | Childhood leukemia | 1986-2008 | | √ | √ | √ |

* a: case control data generated from the original cohort by original author

* Numbers of cases and controls presented in the table are for subjects with available measurements

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Table 2. Absolute numbers of childhood cancer cases and controls by study and exposure level.

| Author                  | Year | Cases | Controls | Electro-magnetic Field Level | OR    | 95% CI       |
|-------------------------|------|-------|----------|-------------------------------|-------|-------------|
| **Leukemia**            |      |       |          |                               |       |             |
| Savitz et al.           | 1988 | 5     | 16       | ≥0.2 μT                       | 1.41  | 0.57–3.50   |
|                         | 31   | 191   | < 0.2 μT |                               | 1.0   |             |
| London et al.           | 1991 | 20    | 11       | ≥0.27 μT                      | 1.48  | 0.66–3.29   |
|                         | 24   | 22    | 0.12–<0.27 μT |                       | 0.89  | 0.43–1.71   |
|                         | 35   | 42    | 0.01–<0.12 μT |                     | 0.68  | 0.39–1.17   |
|                         | 85   | 69    | < 0.01 μT |                               | 1.0   |             |
| Feychting and Ahlbom    | 1993 | 4     | 70       | ≥0.2 μT                       |       |             |
|                         | 1    | 67    | 0.1–<0.2 μT |                         |       |             |
|                         | 19   | 207   | < 0.1 μT |                               |       |             |
| Olsen et al.            | 1993 | 3     | 1        | ≥0.4 μT                       | 6.0   | 0.8–44      |
|                         | 1    | 7     | 0.1–<0.4 μT |                         | 0.3   | 0.0–2.0     |
|                         | 829  | 1658  | Not exposed |                             |       |             |
| Verkasalo et al.        | 1993 | 1     | 7        | ≥0.4 μT                       | 6.21  | 0.68–56.9   |
|                         | 1    | 10    | 0.2–<0.4 μT |                         | 4.11  | 0.48–35.1   |
|                         | 0    | 19    | 0.1–<0.2 μT |                         |       |             |
|                         | 27   | 991   | < 0.1 μT |                               |       |             |
| Linet et al.            | 1997 | 5     | 5        | ≥0.5 μT                       | 1.01  | 0.26–3.99   |
|                         | 10   | 2     | 0.4–<0.5 μT |                         | 6.41  | 1.30–31.73  |
|                         | 14   | 11    | 0.3–<0.4 μT |                         | 1.46  | 0.61–3.50   |
|                         | 29   | 26    | 0.2–<0.3 μT |                         | 1.31  | 0.68–2.51   |
|                         | 107  | 106   | 0.1–<0.2 μT |             | 1.15  | 0.79–1.65   |
|                         | 298  | 313   | < 0.1 μT |                               |       |             |
| Michaelis et al.        | 1997 | 9     | 8        | ≥0.2 μT                       | 2.3   | 0.8–6.7     |
|                         | 165  | 406   | < 0.2 μT |                               |       |             |
| Tynes et al.            | 1997 | 1     | 14       | ≥0.14 μT                       | 0.3   | 0.0–2.1     |
|                         | 8    | 19    | 0.05–<0.14 μT |                     | 1.8   | 0.7–4.2     |
|                         | 139  | 546   | < 0.05 μT |                               |       |             |
| Dockerty et al.         | 1998 | 5     | 1        | ≥0.2 μT                       | 15.5  | 1.1–224     |
|                         | 4    | 5     | 0.1–<0.2 μT |                         | 1.4   | 0.3–7.6     |
|                         | 31   | 34    | < 0.1 μT |                               |       |             |
| Green et al.            | 1998 | 21    | 46       | ≥0.13 μT                       | 1.68  | 0.58–4.82   |
|                         | 27   | 41    | 0.07–<0.13 μT |                     | 1.44  | 0.50–4.16   |
|                         | 19   | 49    | 0.03–<0.07 μT |                     | 1.30  | 0.47–3.55   |
|                         | 15   | 44    | < 0.03 μT |                               |       |             |
| McBride et al.          | 1999 | 8     | 6        | ≥0.5 μT                       | 0.89  | 0.24–3.36   |
|                         | 5    | 8     | 0.4–<0.5 μT |                         | 0.44  | 0.11–1.80   |
|                         | 11   | 9     | 0.3–<0.4 μT |                         | 1.24  | 0.47–3.26   |
|                         | 30   | 29    | 0.2–<0.3 μT |                         | 1.06  | 0.57–1.99   |
|                         | 63   | 95    | 0.1–<0.2 μT |                         | 0.70  | 0.46–1.06   |
|                         | 176  | 192   | < 0.1 μT |                               |       |             |
| UKCCS investigators     | 1999 | 5     | 3        | ≥0.4 μT                       | 1.68  | 0.40–7.10   |
|                         | 16   | 20    | 0.2–<0.4 μT |                         | 0.78  | 0.40–1.52   |
|                         | 57   | 73    | 0.1–<0.2 μT |                         | 0.78  | 0.55–1.12   |
|                         | 995  | 977   | < 0.1 μT |                               |       |             |
| Kleinerman et al.       | 2000 | 35    | 35       | ≥1.3 μT                       | 0.98  | 0.59–1.63   |
|                         | 26   | 36    | 0.66–<1.30 μT |                     | 0.72  | 0.41–1.27   |

(Continued)
Table 2. (Continued)

| Author          | Year   | Cases | Controls | Electro-magnetic Field Level | OR   | 95%CI  |
|-----------------|--------|-------|----------|------------------------------|------|--------|
| Kabuto et al.   | 2000   | 3     | 3        | >0.1 μT                      | 5.81 | 0.78–43.2 |
|                 |        | 6     | 8        | 0.2–<0.4 μT                  | 3.29 | 1.11–9.73 |
|                 |        | 77    | 401      | Not exposed                  |      |         |
| Schüz et al.    | 2001   | 3     | 3        | >0.4 μT                      | 7.81 | 0.43–3.11 |
|                 |        | 6     | 15       | 0.1–<0.2 μT                  | 4.16 | 0.74–1.18 |
|                 |        | 33    | 77       | Not exposed                  |      |         |
| Feizi and Arabi | 2007   | 5     | 5        | ≥0.45 μT                     | 3.56 | 0.37–12.39 |
|                 |        | 45    | 54       | < 0.45 μT                    |      |         |
| Kroll et al.    | 2010   | 2     | 1        | >0.4 μT                      | 2.00 | 0.18–22.04 |
|                 |        | 0     | 2        | 0.2–<0.4 μT                  |      |         |
|                 |        | 6     | 3        | 0.1–<0.2 μT                  | 3.00 | 0.50–7.99 |
|                 |        | 9645  | 9647     | Not exposed                  |      |         |
| Malagoli et al. | 2010   | 2     | 3        | ≥0.1 μT                      | 6.7  | 0.68–78.3 |
|                 |        | 27    | 129      | <0.1 μT                      |      |         |
| Does et al.     | 2011   | 3     | 6        | ≥0.3 μT                      | 0.57 | 0.54–2.36 |
|                 |        | 5     | 6        | 0.2–<0.3 μT                  | 1.03 | 0.30–3.55 |
|                 |        | 22    | 12       | 0.1–<0.2 μT                  | 1.98 | 0.94–4.17 |
|                 |        | 215   | 245      | <0.1 μT                      |      |         |
| Wünsch Filho et al. | 2011 | 11    | 34       | ≥0.3 μT                      | 1.09 | 0.33–3.61 |
|                 |        | 38    | 137      | 0.1–<0.3 μT                  | 0.75 | 0.36–1.55 |
|                 |        | 113   | 394      | <0.1 μT                      |      |         |
| Jirik et al.    | 2012   | 31    | 32       | ≥0.2 μT                      | 0.93 | 0.45–1.93 |
|                 |        | 48    | 47       | <0.2 μT                      | 0.90 | 0.37–2.22 |
|                 |        | 13    | 14       | ≥0.4 μT                      | 0.90 | 0.37–2.22 |
|                 |        | 66    | 65       | <0.4 μT                      |      |         |
| Ba Hakim et al. | 2014   | 11    | 10       | ≥0.3 μT                      | 0.82 | 0.33–2.00 |
|                 |        | 97    | 108      | <0.3 μT                      |      |         |
| Bunch et al.    | 2015   | 2     | 1        | ≥0.4 μT                      | 2.00 | 0.18–22.06 |
|                 |        | 3     | 4        | 0.2–<0.4 μT                  | 0.92 | 0.20–4.17 |
|                 |        | 1     | 1        | 0.1–<0.2 μT                  | 0.80 | 0.07–9.10 |
|                 |        | 17304 | 20952    | <0.1 μT                      |      |         |
| Pedersen et al. | 2015   | 5     | 6        | ≥0.4 μT                      | 1.67 | 0.51–5.46 |
|                 |        | 5     | 13       | 0.1–<0.4 μT                  | 0.77 | 0.27–2.16 |
|                 |        | 1526  | 3053     | <0.1 μT                      |      |         |
| Salvan et al.   | 2015   | 15    | 24       | ≥0.3 μT                      | 0.75 | 0.38–1.50 |
|                 |        | 20    | 13       | 0.2–<0.3 μT                  | 2.24 | 1.03–4.88 |
|                 |        | 39    | 69       | 0.1–<0.2 μT                  | 0.81 | 0.53–1.25 |
|                 |        | 335   | 463      | <0.1 μT                      |      |         |
| Kheifets et al. | 2017   | 17    | 11       | ≥0.4 μT                      | 1.48 | 0.69–3.19 |

(Continued)
Table 2. (Continued)

| Author                | Year   | Cases | Controls | Electro-magnetic Field Level | OR   | 95% CI   |
|-----------------------|--------|-------|----------|------------------------------|------|----------|
| Crespi et al.         | 2019   | 17    | 11       | $>$0.4 μT                    | 1.50 | 0.70–3.23 |
|                       |        |       |          | $>$0.4 μT                    | 0.97 | 0.46–2.02 |
|                       |        |       |          | $<$0.1 μT                    | 0.84 | 0.48–1.46 |
| Lymphomas             |        |       |          |                              |      |          |
| Savitz et al.         | 1988   | 2     | 16       | $>$0.2 μT                    | 1.81 | 0.48–6.88 |
|                       |        |       |          | $<$0.2 μT                    |      |          |
| Olsen et al.          | 1993   | 1     | 1        | $>$0.4 μT                    | 5.0  | 0.3–82   |
|                       |        |       |          | $>$0.1 μT                    | 5.0  | 0.7–36   |
|                       |        |       |          | Not exposed                  |      |          |
| Tynes et al.          | 1997   | 2     | 3        | $>$0.14 μT                   | 2.5  | 0.4–15.5 |
|                       |        |       |          | $<$0.1 μT                    | 1.0  | 0.1–8.7  |
| Pedersen et al.       | 2015   | 2     | 4        | $>$0.4 μT                    | 2.50 | 0.46–13.65 |
|                       |        |       |          | $>$0.1 μT                    | 1.25 | 0.35–4.43 |
| Brain tumor (Central Nervous System) | | | | | | |
| Savitz et al.         | 1988   | 2     | 16       | $>$0.2 μT                    | 0.82 | 0.23–2.93 |
|                       |        |       |          | $<$0.2 μT                    |      |          |
| Feychtning and Ahlbom | 1993   | 5     | 70       | $>$0.2 μT                    | 1.2  | 0.4–3.2  |
|                       |        |       |          | $<$0.2 μT                    | 1.8  | 0.7–4.5  |
|                       |        |       |          | $<$0.1 μT                    | 1.5  | 0.7–3.2  |
| Olsen et al.          | 1993   | 2     | 1        | $>$0.4 μT                    | 6.0  | 0.7–44   |
|                       |        |       |          | $>$0.1 μT                    | 0.4  | 0.1–2.8  |
|                       |        |       |          | Not exposed                  |      |          |
| Preston-Martin et al. | 1996   | 11    | 11       | $>$0.2 μT                    | 1.2  | 0.4–3.2  |
|                       |        |       |          | $>$0.1 μT                    | 1.8  | 0.7–4.5  |
|                       |        |       |          | $<$0.1 μT                    | 1.5  | 0.7–3.2  |
| Tynes et al.          | 1997   | 4     | 23       | $>$0.14 μT                   | 0.7  | 0.7–2.1  |
|                       |        |       |          | $>$0.1 μT                    | 1.9  | 0.8–4.6  |
| UKCCS investigators   | 1999   | 0     | 2        | $>$0.4 μT                    | 1.0  | 0.1–10.1 |
|                       |        |       |          | $>$0.1 μT                    | 0.70 | 0.16–3.17 |
|                       |        |       |          | $>$0.1 μT                    | 2.44 | 1.17–5.11 |
|                       |        |       |          | $<$0.1 μT                    |      |          |
| Kroll et al.          | 2010   | 1     | 3        | $>$0.4 μT                    | 0.33 | 0.0–3.20 |
|                       |        |       |          | $>$0.1 μT                    | 0.33 | 0.0–3.20 |
|                       |        |       |          | $>$0.05 μT                   | 0.50 | 0.09–2.73 |
| Saito et al.          | 2010   | 3     | 1        | $>$0.4 μT                    | 10.9 | 1.05–113 |
|                       |        |       |          | $>$0.05 μT                   | 1.58 | 0.25–9.83 |
|                       |        |       |          | $>$0.1 μT                    | 0.74 | 0.17–3.18 |
|                       |        |       |          | $>$0.1 μT                    |      |          |
quality. The results associated with the quality ratings of the retrieved studies are shown in Table 3. A total score of 7 and more indicated high-quality studies.

### Meta-analysis

We identified 30 studies with 186,233 subjects that report results on the association between ELF-MFs and childhood cancer. Meta-analyses were conducted for pediatric leukemia, brain tumors, and any childhood cancers by level of exposure to ELF-MFS.

#### Childhood leukemia

A total of 27 studies including 45,029 cases and 55,376 controls were included in the meta-analysis for leukemia (Table 2). For a group exposed to 0.2-μT and higher level of ELF-MFs, the association with childhood leukemia was significant (pooled

| Author            | Year | Cases | Controls | Electro-magnetic Field Level | OR    | 95% CI |
|-------------------|------|-------|----------|------------------------------|-------|--------|
| Bunch et al.      | 2015 | 0     | 1        | ≥0.4 μT                      | -     | -      |
|                   |      | 0     | 0        | 0.2-<0.4 μT                  | -     | -      |
|                   |      | 4     | 1        | 0.1-<0.2 μT                  | 4.65  | 0.51–42.23 |
|                   |      | 12294 | 15258    | <0.1 μT                      | -     | -      |
| Pedersen et al.   | 2015 | 4     | 9        | ≥0.4 μT                      | 1.33  | 0.41–4.33 |
|                   |      | 8     | 23       | 0.1-<0.4 μT                  | 1.04  | 0.46–2.36 |
|                   |      | 1312  | 3940     | <0.1 μT                      | -     | -      |

#### Any Childhood cancer

| Author            | Year | Cases | Controls | Electro-magnetic Field Level | OR    | 95% CI |
|-------------------|------|-------|----------|------------------------------|-------|--------|
| Savitz et al.     | 1988 | 13    | 16       | ≥0.2 μT                      | 1.35  | 0.63–2.90 |
| Myers et al       | 1990 | 1     | 4        | ≥0.1 μT                      | 0.39  | 0.04–4.09 |
| Feychting and Ahlbom | 1993 | 16    | 70       | ≥0.2 μT                      | 0.9   | 0.5–1.7   |
| Olsen et al.      | 1993 | 6     | 3        | ≥0.4 μT                      | 5.6   | 1.6–19   |
| Tynes et al.      | 1997 | 12    | 51       | ≥0.14 μT                     | 0.9   | 0.5–1.8   |
| UKCCS investigators | 1999 | 8     | 9        | ≥0.4 μT                      | 0.89  | 0.34–2.29 |
| Pedersen et al.   | 2015 | 11    | 19       | ≥0.4 μT                      | 1.63  | 0.77–3.46 |
|                   |      | 16    | 48       | 0.1-<0.4 μT                  | 0.98  | 0.55–1.74 |

OR = Odds ratio; CI = confidence interval

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Table 3. Newcastle-Ottawa Scale assessment of the quality for the included studies.

| Author                  | Year  | Case Definition | Representativeness of the Cases | Selection of Cases | Definition of Controls | Comparability Ascertainment of Exposure | Same method of ascertainment | Non-Response Rate | Total Scores |
|-------------------------|-------|-----------------|---------------------------------|-------------------|------------------------|----------------------------------------|-----------------------------|-----------------|--------------|
| Savitz et al.           | 1988  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Myers et al.            | 1990  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| London et al.           | 1991  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Feychting and Ahlbom    | 1993  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Olsen et al.            | 1993  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Verkasalo et al.        | 1993  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Preston-Martin et al.   | 1996  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Linet et al.            | 1997  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Michaelis et al.        | 1997  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Tynes et al.            | 1997  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Dockerty et al.         | 1998  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Green et al.            | 1999  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| McBride et al.          | 1999  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| UKCCS investigators      | 1999  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 9            |
| Kleinerman et al.       | 2000  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Bianchi et al.          | 2000  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Schütz et al.           | 2001  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Kabuto et al.           | 2006  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Feizi and Arabi         | 2007  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Kroll et al.            | 2010  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Malagoli et al.         | 2010  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Saito et al.            | 2010  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Does et al.             | 2011  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Wünsch Filho et al.     | 2011  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Jirik et al.            | 2012  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Ba Hakim et al.         | 2014  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Bunch et al.            | 2015  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Pedersen et al.         | 2015  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Salvan et al.           | 2015  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |
| Khelifet et al.         | 2017  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 7            |
| Crespi et al.           | 2019  | ✷               | ✷                               | ✷                 | ✷                      | ✷                                      | ✷                           | ✷               | 8            |

* denotes 1 point. The empty cells indicate that the study did not have any points for that category.
summary OR, 1.26; 95% CI, 1.06–1.49) in a random effect model (Fig 2A) without any significant heterogeneity among studies being shown ($I^2 = 0\%$). For the 0.3-µT exposure level of ELF-MFs, the pooled summary OR was 1.22 (0.93–1.61) without any significant heterogeneity ($I^2 = 0\%$; Fig 2B). For a 0.4-µT exposure level of ELF-MFs, the pooled summary OR was 1.72 (1.25–2.35; Fig 2C).

We checked for the presence of publication bias through a funnel plot and found that there was no evidence of publication bias (Fig 2). With the results shown in the meta-analysis that indicate the risk of childhood leukemia by the exposure level of ELF-MFs, the odds level increased as the exposure level increased (1.26→1.22→1.72), which shows a dose-response effect. This confirms an association between exposure to ELF-MFs and a high risk of childhood leukemia.
Pediatric brain tumor. A total of 10 studies including 21,582 cases and 29,463 controls were included in the meta-analysis of the association between exposure to ELF-MFs and pediatric brain tumors (Table 2). In this study, the meta-analysis was performed by the exposure levels of 0.2 and 0.4-μT. The pooled summary OR for the 0.2-μT exposure level of ELF-MFs was 0.95 (0.59–1.56) in a random effect model, and no significant heterogeneity was detected ($I^2 = 0$%; Fig 3A). This non-significant association was observed for the 0.4-μT exposure level (1.25, 0.93–1.61), and the heterogeneity might not be important ($I^2 = 23$%; Fig 3B). We confirmed through the funnel plot that there was no indication of publication bias for the studies included in our meta-analysis (Fig 3).

Any childhood cancers. The results of six study were used to examine an association of exposure to ELF-MFs with any childhood cancers. The pooled summary OR of the 0.2-μT exposure level of ELF-MFs was 1.10 (0.70–1.75) (Fig 4A), whereas that for the 0.4-μT exposure level was 2.10 (0.70–1.75) (Fig 4B). The size of significant heterogeneity was moderate ($I^2 = 43–49$%), and there was evidence of publication bias (Fig 4).

Sensitivity analysis. The sensitivity analysis was performed after excluding either studies that used calculated fields measurement method or studies that identified very small cases even though many participants were examined and, hence, affected to pooled estimate of meta-analysis significantly [15, 22]. The pooled summary OR for childhood leukemia with 11 studies that directly measured the level of exposure was 1.27 (1.05–1.53) at exposure levels above 0.2-μT, and 1.44 (0.95–2.17) at exposure levels above 0.4-μT in 6 studies. Excluding 2 studies with very small cases [15, 22], the pooled summary OR of 12 studies was 1.27 (1.07–1.51) at above 0.2-μT, and 1.70 (1.24–2.34) at above 0.4-μT.

Discussion
We conducted a meta-analysis on each type of cancer to derive the large-scale integrated values for the association between ELF-MFs exposure and childhood cancer among more than 85,000 children diagnosed with childhood cancer in 15 countries. In this study, based on the
systematic review methodology, all articles that presented pediatric cancer, including leukemia, lymphoma, and brain tumor, were included in a comprehensive search. Pooled analysis studies have been conducted on the association between childhood cancer and ELF-MFs exposure [4, 5, 14, 59]. However, such studies did not include articles that were identified through a comprehensive search, and pooled analyses were performed by using a modified level of exposure to ELF-MFs. In this regard, this study is the first to conduct a systematic review of the association between ELF-MFs exposure and childhood cancer, and to have rigorously performed a meta-analysis. Additionally, while previous pooled analyses had been performed with 2 to 10 studies, this study expands the results using up to date 30 studies.

The existence of between-study heterogeneity can generate a statistical problem when attempting to interpret the results of the meta-analysis. Ideally, the studies, whose results are being combined in the meta-analysis, should all be undertaken in the same way and with the same experimental protocols: study heterogeneity is a term used to indicate that this ideal is not fully met [27]. Meta-analysis is a method for combining the results of different studies to obtain a quantified synthesis, and it increases the power of statistical analyses by pooling the results of all available studies. A meaningful explanation is possible when attempting to estimate the combined effect of a similar study group by using meta-analysis, and the presence of heterogeneity can affect the statistical validity of the estimated summary of that effect [60]. The results of the present study are meaningful because the meta-analysis was conducted for the type of childhood cancer that occurred by the exposure levels of ELF-MF—that is, integrated into the random effects model because of potential unexplained heterogeneity [27].

This study showed that children exposed to 0.2-μT ELF-MFs had a 1.26 (95% CI 1.06–1.49) times higher odds of child leukemia, those exposed to 0.3-μT had a 1.22 (0.93–1.61) times higher odds, and those exposed to 0.4-μT had a 1.72 (1.25–2.35) times higher odds. These results are based on statistical homogeneity ($I^2 = 0\%$) as well as an absence of any evidence for publication bias. In addition, this study derived a large-scale integrated value using larger number of included studies than previous studies. Our results showed slightly higher pooled estimates than previous results, which are 1.07–1.08, 1.11–1.16, and 1.44–2.00 times higher.
odds for exposures to 0.2-, 0.3-, and 0.4-μT, respectively [5, 14]. Furthermore, the higher degree of intensity of the association between the exposure to ELF-MFs and childhood leukemia than previous studies was obtained because we observed the dose–response effects of an increase in the pooled OR value with increasing exposure level to ELF-MFs was observed.

According to the pooled OR of 10 studies with 7,247 subjects, children exposed to 0.2-μT ELF-MFs had a 0.95 (0.59–1.56) times higher odds of childhood brain tumors, and children exposed to 0.4-μT ELF-MFs had a 1.25 (0.93–1.61) times higher odds. However, the estimates were not statistically significant. Based on previous pooled analysis, studies showed a 0.95 times on exposure to 0.2-μT and 1.14-times higher odds on exposure to 0.4-μT ELF-MFs, and similar results were found in this study [4].

According to the pooled OR value of four studies, children exposed to 0.2-μT ELF-MFs had a 1.10 (0.70–1.75), and those exposed to 0.4-μT ELF-MFs had a 2.01 (0.89–4.52) times higher odds of any childhood cancer. However, it did not show a high-intensity relation. There have been no pooled analysis studies of any childhood cancer conducted thus far.

Public concern about EMFs is considerably high, and many countries have implemented a lot of policies related to EMFs [61, 62]. Any change in the epidemiological evidence for childhood cancer would be important to these public policies besides the scientific interest that it would generate. Therefore, this study presents the epidemiological evidence of childhood cancer risk on exposure to ELF-MFs, which implies that we can confirm the risk of childhood leukemia among pediatric cancers followed exposure to ELF-MFs, which is associated with a higher risk than what was previously known.

Limitations

Although we identified three cohort studies that met the study eligibility criteria, these studies were not able to include in the meta-analysis. In the cohort study, the incident ratio of childhood leukemia was 1.6 and any childhood cancer was 1.5 in the group exposed to 0.2-μT, however, it was not statistically significant [38]. In the other two studies, the hazard ratio was 1.6 in the group exposed to 0.2-μT [50] and 1.9 in the group exposed to 0.3-μT [57], however, it was also not statistically significant. As the WHO recommends the conducting of cohort studies on EMF health effects, and several large-scale cohort studies are currently ongoing [62], we hope to derive an integrated value of cohort results through a systematic review in the future.

The ELF-MFs measurement variation was not considered in our meta-analysis. Although some studies used a long-term measurement, others used a spot measurement; however, no distinction has been made in our meta-analysis because of the limited number of studies. Nonetheless, our pooled results showed a non-significant heterogeneity among studies.

Another limitation is that all studies included in our study were case-control studies, which reduces the strength of the obtained results because case–control studies are subject to selection bias and other methodological problems. However, all studies that were included in this meta-analysis were the matched case-control studies except one, which had the case and control groups from the same registry. Therefore, it can be seen that the bias shown in case-control studies has diminished.

Conclusions

In this large pooled analysis of more than 36,000 children diagnosed with childhood leukemia, statistically significant associations were observed between exposure to ELF-MF and childhood leukemia. Furthermore, the intensity of the association between exposure to ELF-MFs and childhood leukemia was high, as indicated by the dose–response effect.
The risk of ELF-MFs, which have been classified as a possibly carcinogenic (Group 2B) factor based on limited evidence in humans, can be ascertained through precise evidence from the integrated results of this study.

Supporting information

S1 Table. Search strategy in databases. Search strategies and search results for each database (Pubmed, Embase, Web of Science).

S1 Checklist.

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