

Review

Childhood Leukemia and EMF: Review of the Epidemiologic Evidence

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All populations are exposed to varying degrees of electromagnetic fields (EMF); in this study we consider only extremely low frequency (ELF) and radio frequency (RF) fields. After the first study of ELF and childhood leukemia in 1979, intensive epidemiologic investigation has sought to shed light on the potential relation between EMF and childhood leukemia. Consistent associations from epidemiologic studies and two pooled analyses have been the basis for the classification of ELF as a possible carcinogen by the International Agency for Research on Cancer (IARC). The study of RF is still in its infancy and little is known about residential RF exposure or its potential effects on childhood leukemia. The purpose of this study, presented at the WHO Workshop on Sensitivity of Children to EMF in Istanbul, Turkey in June 2004, is to review and critically assess the epidemiologic evidence on EMF and childhood leukemia. Bioelectromagnetics Supplement 7:S51–S59, 2005. © 2005 Wiley-Liss, Inc.

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INTRODUCTION

Childhood leukemia has remained a focal point of extensive etiologic, diagnostic, and therapeutic research since its recognition as a clinical entity over a century ago [Pinkel, 1993]. It is one of the most common cancers in children, comprising more than a third of all childhood cancers [Greenberg and Shuster, 1985]. The age standardized rate of leukemia for children younger than 15 years has been estimated to be 3.5 per 100 000 per year for females and 4.2 per 100 000 per year for males in the developed world, 2.2 per 100 000 per year for females, and 2.9 per 100 000 per year for males in the developing world [IARC, 2000].

Leukemia results from chromosomal alterations and mutations that disrupt the normal process by which lymphoid or myeloid progenitor cells differentiate. The underlying triggers for molecular damage may be inherited at conception, may occur during fetal development or during infancy (see T. Lightfoot in this issue for details). Most likely there is an accumulation of a series of detrimental genetic changes over time. Though there have been significant advances in diagnostic techniques and improvements in treatment, most of the etiology of leukemia in children is unknown.

A wide variety of factors have been hypothesized to be involved in the etiology of childhood leukemia. Among environmental exposures possibly associated with childhood leukemia, ionizing radiation is a generally accepted risk factor [Bhatia et al., 1999]. The list of chemical agents for which some evidence points to a

link with leukemogenesis includes solvents, pesticides, tobacco smoke, and certain dietary agents. The possible role of viral or other infectious agents in triggering leukemia development has also been hypothesized [Mezei and Kheifets, 2002]. Generally accepted associations, however, explain only 10% of childhood leukemia incidence [Ichimaru et al., 1978], leaving the majority with unexplained etiology.

Consistent epidemiologic evidence demonstrates a small risk of extremely low frequency (ELF) electromagnetic fields (EMF) on childhood leukemia, thus leading to an International Agency for Research on Cancer (IARC) classification of ELF as a “possible” or 2B carcinogen in 2002. As compared to the ELF literature, research on the potential health effects of radio-frequency (RF) EMF is still in its infancy and studies to date have been uninformative. The purpose of this study is to present the epidemiologic literature on EMF and childhood leukemia, and to discuss possible

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explanations for the observed ELF and childhood leukemia association.

EPIDEMIOLOGIC STUDIES OF ELF AND CHILDHOOD LEUKEMIA

The study by Wertheimer and Leeper [1979] was the first epidemiologic study to examine the relation between EMF and childhood leukemia. They developed a metric called wire codes as a proxy for exposure to EMF; it considers the likely current load carried by electrical power lines outside homes as indicated by the thickness of the wires and different wiring configurations, for example the location of transformers and the proximity of the lines to the home. In their analysis of childhood leukemia and wire codes, there were more reported cases of childhood leukemia in homes with high-current configurations than in those with low-current configurations. Since this first study, there have been over 20 studies examining this association. Epidemiologic studies of ELF and childhood leukemia are difficult to design, conduct and interpret for a number of methodologic reasons. EMF are imperceptible, ubiquitous, have multiple sources, and can vary greatly over time and short distances [Bracken et al., 1993]. Also, the small number of leukemia cases available in any given population necessitates retrospective design, making exposure assessment even more difficult.

After the development of EMF measurement instruments, a small number of studies used spot measurements under varying household power use conditions. Later, studies included both 24–48 h measurements in the child's bedroom as well as shorter measurements in other areas inside and outside the home (see Table 1): [Tomenius, 1986; Savitz et al., 1988; London et al., 1991; Coghill et al., 1996; Linet et al., 1997; Michaelis et al., 1997; Dockerty et al., 1999; Green et al., 1999a; McBride et al., 1999; UK Childhood Cancer Study Investigators, 1999; Ahlbom et al., 2000; Schuz et al., 2001; Kabuto et al., 2005]. Some studies have used calculated fields, based on a number of variables that often include distance of home to a transmission line and current phases and loads (see Table 1): [Myers et al., 1990; Feychting and Ahlbom, 1993; Olsen et al., 1993; Verkasalo et al., 1993; Tynes and Haldorsen, 1997; Bianchi et al., 2000]. While ELF exposure assessment can be deemed one of the most important tasks in epidemiologic studies, it remains one of the biggest challenges. The assessment of exposure to magnetic fields has improved over time, yet our ability to predict exposure remains severely limited. It has been suggested that EMF exposure assessment might be more accurate for children than for

adults since children spend more time at home and do not have occupational exposures [Forsen et al., 2002].

Inadequate sample size is another methodological challenge: there are few people at or above exposure levels at which most associations between EMF and childhood leukemia are observed, that is above 0.3 or 0.4 μT , that obtaining statistically stable estimates of effect is virtually impossible. Although many studies have attempted to include large sample sizes, any study is only as big as its smallest cell, which is most often the cell containing the highly exposed leukemia cases. For instance, in the UK study that involved 1094 cases and 1096 controls, only 5 cases and 3 controls were observed at levels greater than 0.4 μT [UK Childhood Cancer Study Investigators, 1999]. Some studies have had cases but no controls in the highest exposure categories, suggesting elevated risk in these categories, but making odds ratios (ORs) inestimable [Coghill et al., 1996; Dockerty et al., 1999]. One study, however, had no cases but several controls in the highest group [Tynes and Haldorsen, 1997].

Although many epidemiologic studies have observed ORs of above 1.5 (some around 4) for the exposure categories above 0.3 or 0.4 μT as compared to the lowest exposure category of $<0.1 \mu\text{T}$, most are not statistically significant. The only two studies with OR estimates below one have serious methodologic limitations and/or are based on small numbers [Fulton et al., 1980; Myers et al., 1990]. Small effect estimates are notoriously hard to evaluate because it is difficult to achieve enough precision to distinguish a small risk from no risk, and small effect estimates are more likely to result from misclassification, unmeasured, confounding, and selection bias, all of which often go undetected and unmeasured.

Given the small-observed associations, a limited understanding of causal risk factors for childhood leukemia, and methodological difficulties such as exposure assessment, a conclusive interpretation of these studies remains a challenge. Two pooled analyses represent the most powerful attempt so far to provide a cohesive assessment of the epidemiologic data [Ahlbom et al., 2000; Greenland et al., 2000]. These analyses, while focusing on a largely overlapping but distinct set of studies, come to similar conclusions (see Table 1 for details on the studies included in each pooled analysis).

In the pooled analysis by Greenland et al. [2000], 12 studies using measured or calculated fields were identified. For this analysis, the metric of choice was the time-weighted average; and it included a total of 2656 cases and 7084 controls. The estimated OR for childhood leukemia was 1.68 (95% CI 1.23, 2.31) for

TABLE 1. Epidemiologic Studies on the Association Between EMF and Childhood Leukemia

Reference	Measurement	>0.3 μT^{a}		$\geq 0.4 \mu\text{T}^{\text{b}}$	
		Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
Tomenius [1986]	Spot measurement: max. uniaxial value outside front door	3/9	1.5 (0.4–5.7)		
Savitz et al. [1988]	Spot measurements: arithmetic mean of low-power measurement in three locations (child's bedroom, parent's bedroom, other room occupied by child >1 h/day, front door)	3/5	3.5 (0.8–15.4)		
Myers et al. [1990] ^c	Calculated fields				
London et al. [1991]	24 h child bedroom measurement	17/10	1.6 (0.7–3.5)		
Feychting and Ahlbom [1993]	Calculated fields	6/22	4.5 (1.7–12.0)	5/20	3.7 (1.2–11.4)
Olsen et al. [1993]	Calculated fields	3/3	2.0 (0.4–10.0)	2/0	N/A
Verkasalo et al. [1993]	Calculated fields	1/5	2.0 (0.2–18.0)	1/7	6.2 (0.7–56.9)
Coghill et al. [1996]	Night-time child bedroom measurement	1/0	N/A		
Linet et al. [1997]	24 hr bedroom measurement, weighted by spot measurements in other rooms	42/28	1.5 (0.9–2.4)	17/5	3.4 (1.2–9.6)
Tynes and Haldorsen [1997]	Calculated fields	0/31	N/A	0/10	N/A
Michaelis et al. [1997]	24 h child bedroom measurement	6/6	2.4 (0.8–7.6)	2/2	2.0 (0.3–15.2)
Dockerty et al. [1999]	24 h child bedroom measurement	3/0	N/A	0/0	N/A
Green et al. [1999a] ^c	48 h personal measurement				
McBride et al. [1999]	24 h bedroom	14/11	1.4 (0.6–3.2)	13/10	1.6 (0.7–3.7)
UK Childhood Cancer Study Investigators [1999]	Two phase measurement, 48 h home measurement if shorter measurement or other indication showed high EMF	5/3	1.7 (0.4–7.0)	5/3	1.0 (0.3–3.4)
Bianchi et al. [2000] ^c	Calculated fields				
Schuz et al. [2001]	24 h child bedroom measurement			3/3	5.9 (0.8–44.1)
Kabuto et al. [2005]	1 week child bedroom measurement	11/13	1.7 (0.7, 3.8)	Not reported	2.6 (0.8–8.9)

^aEstimates from Greenland et al. [2000] shaded in light gray; UK Childhood Cancer Study Investigators [1999] and Kabuto et al. [2005] have been added to pooled analysis in Greenland [2005]; Reference category <0.1 μT .

^bEstimates from Ahlbom et al. [2000] shaded in dark gray; Reference category <0.1 μT .

^cEstimates that do not use >0.3 μT or $\geq 0.4 \mu\text{T}$ categories. Myers et al. [1990]: for $\geq 0.1 \mu\text{T}$ (1 case/4 controls) compared to <0.01 μT , OR = 0.4 (0.04–4.33). Green et al. [1999a]: for $\geq 0.14 \mu\text{T}$ (29 cases/33 controls) compared to <0.03 μT , OR = 4.5 (1.3, 15.9). Bianchi et al. [2000]: for >0.1 μT (3 cases/3 controls) compared to <0.001 μT , OR = 4.5 (0.9, 23.2).

exposures greater than 0.3 μT as compared to exposures less than 0.1 μT , controlling for age, sex, and study.

Using more stringent inclusion criteria, Ahlbom et al. [2000] included nine studies using measured and calculated fields. There were a total of 3203 cases and 10338 controls in the pooled sample. In this analysis, using the geometric mean as the metric of choice the estimated OR for childhood leukemia was 2.00 (1.27, 3.13) for exposures greater than or equal to 0.4 μT as compared to exposures less than 0.1 μT , controlling for age, sex, socioeconomic status (SES) (in measurement studies only), and East/West (in German study only).

POSSIBLE EXPLANATIONS

The observed associations between childhood leukemia and magnetic field exposure above 0.3–0.4 μT can be due to chance, selection bias, misclassification, or other factors which confound the observed asso-

ciation between exposure and disease. Below we will discuss each of these interpretations in turn.

Chance

Both pooled analyses were based on large numbers and hence resulted in tight confidence intervals. When compared, they demonstrate consistency in the size of their effect estimates and range of confidence intervals. It appears unlikely that random variability (or chance) played a role in the observed effect estimates of both pooled analyses; in his analysis of biases and random error, Greenland [2005] estimates that the probability of random error explaining the observed association is 0.0001.

Selection Bias

In studies of ELF and childhood leukemia, selection bias has been proposed as an explanation for the observed association or at least accounting for part of it

[IARC, 2002]. Selection bias occurs when the probability of being included relates to both exposure and disease, that is, there is differential participation by cases and controls and when exposure status impacts participation. Case-control studies that rely on in-home measurements are especially vulnerable to this bias because selection might operate both at the point of initial enrollment and again when measurements are made. While some studies do in fact report response rates, accurate response rates are not available for all studies. Participation rates often depend on the type of study, with reported rates of 94%–100% in registry based studies, 37%–68% among eligible participants interviewed, and 9%–31% with measurements in matched analysis [Mezei and Kheifets, in preparation]. Hence, the potential for bias is low in registry-based studies and high in studies using measurements.

It is hypothesized that selection bias occurs through SES or mobility, either because participation is higher for high SES controls than for low SES controls because high SES children are less likely to be highly exposed than are low SES children, or because high mobility controls are both less likely to be included and more likely to have high exposure than low mobility controls, leaving a group of controls included in the study with lower exposure levels than would be in a representative group of children without leukemia. Under these scenarios, selection bias upwardly biases the effect estimate. However, most of the available information on SES and mobility is either based on ecological studies or studies of wire code, for example, a study on the association between family income and wire codes [Gurney et al., 1995] and a study reported that people who changed addresses more frequently were more likely to live at addresses with higher wire codes [Jones et al., 1993]. Little is known to what extent measured fields are correlated with either SES or mobility; both German and US studies showed that lower income tended to be associated with higher magnetic field exposure.

The strongest evidence for selection bias comes from a US study in which exclusion of partial participants from analyses tended to increase the risk estimates for childhood leukemia [Hatch et al., 2000]. The strongest evidence against the selection bias comes from Ahlbom et al. [2000] pooled analysis. The studies conducted in the Nordic countries, not requiring subject participation due to the use of calculated magnetic fields measurements, are not subject to selection bias. Taking advantage of this fact, investigators compared risk estimates in Nordic studies to the rest of the world and found similar estimates (OR = 2.1, 0.9–4.9 and OR = 1.9, 1.1–3.2, respectively). Another argument against selection bias is that there is an apparent lack of

a consistent association in studies of childhood brain tumors and residential magnetic fields. Many of the leukemia studies included in the pooled analysis examined brain tumors as well and there is no reason to think that selection bias would affect one outcome and not the other. However, this conclusion is tentative since there are fewer and smaller brain tumor studies, and a pooled analysis of brain tumor studies is yet to be conducted [Kheifets, 2001].

Understanding the impact of selection bias on effect estimates from case-control studies remains a high priority, not only for clarifying the association between magnetic field exposure and leukemia, but also because of its general importance to the field of epidemiology.

Misclassification Bias

All of the difficulties with ELF exposure assessment are likely to have led to substantial exposure misclassification, which, in turn, is likely to interfere with detection of an association between exposure and disease. Almost certainly, measurement errors in both measured and calculated fields are not only present in all studies but also vary considerably from study to study. Target exposure, often described as the average exposure during the period prior to disease diagnosis, is not measured consistently among studies. Furthermore, measured exposure probably does not reflect the biologically relevant exposure, which remains unknown.

It is generally assumed that misclassification in ELF and leukemia studies is non-differential [IARC, 2002] that exposure misclassification does not differ by disease status. Non-differential misclassification translates into a bias of the effect estimate towards the null in most situations, although misclassification in middle categories can lead to the distortion of the dose-response curve.

Pooled analyses points to the occurrence of an effect of ELF on leukemia at high levels of exposure, described as greater than 0.3 or 0.4 μT . In the pooled analysis by Ahlbom et al. [2000] estimated relative risks for childhood leukemia with mean residential magnetic field exposure were: OR = 1.08 (95% CI = 0.89–1.31) for 0.1–0.2 μT , OR = 1.11 (0.89–1.47) for 0.2–0.4 μT , OR = 2.00 (1.27–3.13) for above 0.4 μT , all relative to exposure below 0.1 μT . In the pooled analysis by Greenland et al. [2000], the OR was 1.01 (0.84–1.21) for 0.1–0.2 μT and 1.06 (0.78–1.44) for 0.2–0.3 μT , while for exposures greater than 0.3 μT the OR was 1.68 (1.24–2.31), all compared to exposure less than 0.1 μT .

Since there is no established gold standard for the biologically relevant exposure, neither sensitivity (ability to correctly identify exposed individuals in a

population) nor specificity (ability to correctly identify unexposed individuals in a population) of the measurement tool used to characterize exposure can be determined. We do know, however, that the specificity is particularly important for rare exposures; even a small decrease in specificity (less than 5%) can reduce a risk ratio estimate of five to an observed risk of less than two (J. Schuz, personal communication, 2004). A similar reduction in sensitivity has only a small effect on the risk estimate. For magnetic fields, identifying the unexposed as such is difficult.

According to Greenland [2005], while misclassification is likely to be ever-present, it is unlikely to solely provide an explanation for the observed association; it does, however, introduce a great deal of uncertainty into the potential dose-response.

Confounding

Since the early days of EMF research, investigators have searched for possible confounding factors that can explain the observed associations. The hypothesized confounders of the relation between ELF and childhood leukemia include socio-economic status, residential mobility, residence type, viral contacts, environmental tobacco smoke, dietary agents, and traffic density [Savitz et al., 1988; London et al., 1991; Linet et al., 1997; Michaelis et al., 1997; Green et al., 1999a,b; McBride et al., 1999; UK Childhood Cancer Study Investigators, 1999, 2000; Schuz et al., 2001]. None of these variables have been found to confound the association, although some have been identified as potential risk factors. For a factor to be a confounder it has to exert an effect considerably larger than the observed association and be strongly correlated with exposure. A confounder can obscure or distort the statistical association between exposure and disease. Owing to limited knowledge of the etiology of childhood leukemia and an absence of strong risk factors, it is not surprising that substantial confounding has not been identified. The same observation, however, makes it difficult to exclude the possibility of a yet-to-be-identified confounder or some combination of confounding factors. Nevertheless, substantial confounding of the observed association seems unlikely.

Multiple-Bias Modeling

The observed ELF and childhood leukemia associations from epidemiologic studies are clearly difficult to interpret due to the high degree of uncertainty regarding the influence of potential biases. With such small relative risks, it is possible that one or a combination of the biases can explain the observed associations. In pooled analyses, where random error

is not the only source of uncertainty, uncertainty from biases can be modeled using multiple-bias modeling [Greenland, 2005]. Multiple-bias modeling is used to systematically integrate the major sources of uncertainty into the results to provide a more unbiased estimate of effect and can be used as a tool to better understand the impact of the different types of biases on the effect estimate.

Greenland [2005] performed multiple-bias modeling using the data from Greenland et al. [2000] pooled analysis, updated with data from two studies [UK Childhood Cancer Study Investigators, 1999; Kabuto et al., 2005]. He concludes that while selection bias is present, it is unlikely to explain the association; that confounding is probably less important than selection bias; and that allowing for misclassification tends to increase the point estimate of risk, but also increases the standard deviation, resulting in less certainty that there is a positive association, but a higher certainty that the effect estimate is large. In other words, misclassification greatly increases uncertainty, making both no association and a strong association more plausible. Greenland [2005] estimates the probability that the combination of misclassification, selection bias, confounding, and random error, or the net impact, explains the observed association of 2%–4%. Other plausible assumptions would yield different results. The point of this analysis, however, is that the studies completed through 2003 are not decisive because of their design limitations and further studies of similar design would add little information.

Other Hypotheses

The absence of a clearly elucidated, robust, and reproducible mechanism of interaction of low-level magnetic fields with biological systems deprives epidemiologic studies of focus in their study designs and hinders the interpretation of the results. Based on known physical principles and a simplistic biological model, it has been argued that average magnetic fields of 0.3–0.4 μT are orders of magnitude below levels that could interact with cells or tissues and that such interactions are thus biophysically implausible [NRC, 1997; Portier and Wolfe, 1998; NRPB, 2001, 2003; Neutra et al., 2002]. Kavet and Zaffanella [2002] argue that exposure to contact currents are capable of overcoming this “implausibility” argument; (see R. Kavet in this issue for details): an open-circuit voltage (V_{OC}) may exist on the surfaces of appliances or plumbing, and if a person comes in contact with such a surface a minute amount of current can flow into the body. This hypothesis is based on theoretical calculations that show a high correlation between residential magnetic fields and V_{OC} . A dosimetry model suggests that very

small currents can produce a dose in the bone marrow of a child that is much higher than the dose produced by high average residential magnetic field exposure. Furthermore, this predicted dose is higher than the dose at which biological effects relevant to carcinogenesis have been observed.

Another hypothesized biological mechanism is the potential link between ELF and serum melatonin level and, in turn, its postulated association with leukemia risk [Schuz et al., 2001] (see Henshaw et al. in this issue for details). This hypothesis is based on the observation that, in some studies in adults, chronic exposure to ELF reduces and/or disrupts the nocturnal production of melatonin. A stronger association between night-time exposure (as compared to 24 h) and childhood leukemia has been observed. Melatonin has been proposed to be a radical scavenger and antioxidant, and to be protective of oxidative damage to the human hematopoietic system. Hence, serum melatonin levels have been suggested to be biologically relevant to the development of leukemia.

Lastly, research has also focused on identifying children genetically susceptible to leukemia and understanding the interaction between genetic susceptibility and environmental exposure on leukemia risk. Chromosomal translocations have been shown to initiate leukemia in utero [Greaves, 2002]. A “second-hit” is hypothesized as needed to complete disease progression and cause leukemia (see T. Lightfoot in this issue for more details). Magnetic fields might be one of the exposures involved in the later stages of leukemogenesis.

All of these hypotheses remain speculative and are motivated by a need to explain the observed association between magnetic field and childhood leukemia.

Causality

Epidemiologic studies of magnetic fields have consistently found an association between ELF and childhood leukemia, but lack of a known mechanism at such low energy levels and negative animal data detract from a conclusion that the ELF and childhood leukemia association is causal [IARC, 2002].

In vitro studies on the possible carcinogenicity of electric and magnetic fields have investigated a variety of processes in a number of cell lines and tissue cultures, under a wide range of exposure conditions. Since ELF do not appear to initiate cancer, researchers have hypothesized that they may act as a cancer promoter or progressor. In vitro research on the carcinogenicity of ELF has been plagued by a lack of consistency and reproducibility. Of the approaches to evaluating ELF as a potential health hazard, toxicologic experiments provide the most consistently negative data [Portier

and Wolfe, 1998]. In particular, data on leukemia in experimental animals is negative [IARC, 2002].

However, even consistent negative toxicologic data cannot completely overcome consistent epidemiologic studies. First, a good animal model for childhood leukemia has been lacking. Second, particularly for ELF, the complex exposures that humans encounter on a daily basis and a lack of understanding of the biologically relevant exposure calls into question the relevance of exposures applied in toxicology. Another limitation of toxicologic studies is that animals cannot be exposed to fields that are orders of magnitude more powerful than those encountered by humans, decreasing their power to detect small risks.

It is worth mentioning that epidemiologic data appears to be not only consistent, but also specific. For cancer, the observed association seems to be limited to leukemia, and even more specifically to childhood leukemia. Several explanations can be advanced to explain the lack of an association with adult leukemia. One possibility is that, as mentioned above, exposure assessment methods used are much better in capturing exposure of children than that of adults. Of more interest to the WHO Workshop on Sensitivity of Children to EMF is the possibility that children are more vulnerable to magnetic fields due to, for example, the timing of exposure relevant to their development or predisposition due to an initiating event that occurred in utero.

The classification of ELF as a “possible human carcinogen” by IARC was based on consistent epidemiological evidence of an association between exposure to these fields and childhood leukemia and laboratory studies in animals and cells, which were not supportive of exposure to ELF causing cancer [IARC, 2002]. Although the body of evidence is always considered as a whole, based on the weight of evidence approach and incorporating different lines of scientific enquiry, epidemiologic evidence, as most relevant, is given the greatest weight.

EPIDEMIOLOGIC STUDIES OF RF AND CHILDHOOD LEUKEMIA

RF fields are produced by radio and TV broadcast towers, mobile phone base stations, and other communications infrastructure. Several ecological studies or cluster investigations have examined cancer risk, including risk of childhood leukemia, among populations in proximity to radio and television broadcast towers [See Table 2: Selvin et al., 1992; Maskarinec et al., 1994; Hocking et al., 1996; Dolk et al., 1997; McKenzie et al., 1998; Cooper et al., 2001]. A recent study looked at mortality from cancers in areas of close

TABLE 2. Epidemiologic Studies on the Association Between RF and Childhood Leukemia*

Reference	Exposure	No. cases	OR (95% CI)
Selvin et al. [1992]	Microwave antenna, internal comparison	52	N/A; analysis of spatial data
Maskarinec et al. [1994]	Low-frequency radio, <2.6 miles	12	2.0 (0.1–8.3)
Hocking et al. [1996]	TV antenna, inner/outer	—	1.6 (1.1–2.3)
Dolk et al. [1997]	TV and FM radio, <2 km	10	1.1 (0.6–2.0)
McKenzie et al. [1998]	TV antennas, continuous ($\mu\text{W}/\text{cm}^2$)	—	0.9 (0.6–1.4)
Cooper et al. [2001]	TV and FM radio, <2 km	1	1.1 (0.0–6.3)
Michelozzi et al. [2002]	Radio station, <6 km	8	2.2 (1.0–4.1)

*Adapted from Ahlbom et al. [2004].

proximity to radio broadcasting towers [Park et al., 2004]. These analyses are mostly based on distance from the source and include small number of cases. Hence, such studies have been largely uninformative: the results are inconsistent and most studies are limited by small sample size, lack of any information on exposures, short follow up periods, and the limited ability to deal with potential confounders. There may be substantial biases in study design, since much of the epidemiologic research has been conducted in response to concerns, either based solely on the exposure source or on a perceived cancer cluster among persons living in the vicinity.

Due to the recent development of technologies using radio frequencies, there is an emerging interest in RF and childhood leukemia. There are unique methodological challenges to its study, because RF fields are harder to characterize than ELF fields; and RF signals from new wireless technologies involve increasingly complex frequency and modulation patterns. Exposure assessment methodology for RF fields, including the development of an RF meter, is still in its infancy. Rapid changes in technology and exponential increase in its use make exposure assessment both more difficult and more urgent.

FURTHER RESEARCH

The ELF and leukemia association has been studied extensively and further studies of similar design are unlikely to provide new insights; only studies that can substantially improve exposure assessment and/or identify highly exposed persons or susceptible subgroups can be informative. The question of selection bias should be further investigated, particularly the relationship between magnetic fields, SES, mobility, and participation. Ultimately, selection bias can only be resolved with large well-conducted cohort studies or with case-control studies in which exposure information can be collected independently. However, the rarity of both childhood leukemia and exposure (magnetic

fields above 0.3–0.4 μT) will require either a prohibitively expensive study or an innovative study design.

Pooled analyses for childhood leukemia have been extremely informative and should be extended to include new childhood leukemia studies. Although new studies are unlikely to fundamentally change results of the previous pooled analyses, recent [Schuz et al., 2001; Kabuto et al., 2005] and ongoing studies, such as those currently underway in Italy and the United Kingdom, will add information from more countries and add to the number of highly exposed cases, allowing further investigation. For example, it might be possible to further explore the high end of the dose-response curve and risk modifiers such as age. Similarly, a pooled analysis of brain cancer studies can provide insight into existing data.

Current exposure assessment is particularly weak for base stations, and TV and radio towers. Improved exposure assessment and the development of RF exposure meters are critical steps to better capture exposure from these sources and to determine the feasibility of epidemiologic studies of leukemia in children living in the vicinity of these sources. In addition, it has been suggested that mobile phones are an important source of EMF exposure, particularly to bone marrow in the hands of children. If indeed there is a high potential for exposure to the hand, an epidemiologic study of childhood leukemia among young mobile phone users should be considered.

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