Epidemiologic Studies of Electric and Magnetic Fields and Cancer: Strategies for Extending Knowledge

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Epidemiologic research concerning electric and magnetic fields in relation to cancer has focused on the potential etiologic roles of residential exposure on childhood cancer and occupational exposure on adult leukemia and brain cancer. Future residential studies must concentrate on exposure assessment that is enhanced by developing models of historical exposure, assessment of the relation between magnetic fields and wire codes, and consideration of alternate exposure indices. Study design issues deserving attention include possible biases in random digit dialing control selection, consideration of the temporal course of exposure and disease, and acquisition of the necessary information to assess the potential value of ecologic studies. Highest priorities are comprehensive evaluation of exposure patterns and sources and examination of the sociology and geography of residential wire codes. Future occupational studies should also concentrate on improved exposure assessment with increased attention to nonutility worker populations and development of historical exposure indicators that are superior to job titles alone. Potential carcinogens in the workplace that could act as confounders need to be more carefully examined. The temporal relation between exposure and disease and possible effect modification by other workplace agents should be incorporated into future studies. The most pressing need is for measurement of exposure patterns in a variety of worker populations and performance of traditional epidemiologic evaluations of cancer occurrence. The principal source of bias toward the null is nondifferential misclassification of exposure with improvements expected to enhance any true etiologic association that is present. Biases away from the null might include biased control selection in residential studies and chemical carcinogens acting as confounders in occupational studies. — Environ Health Perspect 101(Suppl 4):83–91 (1993).

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Introduction

A number of reviews of the epidemiologic literature on electric and magnetic fields and cancer have been developed over the last several years. In contrast to substantive reviews that seek to summarize evidence and draw conclusions (*1,2*) or those that explore methodologic issues to assist in drawing conclusions about the evidence (*3,4*), this paper has the limited goals of defining current knowledge for the purpose of identifying gaps that future epidemiologic studies can fill.

Residential Exposure to Magnetic Fields and Cancer

Synopsis of Evidence

Wertheimer and Leeper (*5*) were the first to consider a possible relation between residential exposures to magnetic fields and cancer. They found that children who had died of cancer lived in homes imputed to have elevated magnetic fields based on wiring configuration codes more frequently than controls. Power lines in the vicinity of the home were examined to estimate current flow and distance to the homes as a marker of long-term average magnetic field levels in the home.

The approach to classifying wiring was presented in greater detail in a study of adult cancer (*6*) and has been used, with little modification, in several subsequent studies. Observable characteristics of the power lines serve as the basis for estimating the typical current flow along the lines in order to assign a wiring class based on such factors as the number of phases, the thickness of the wires, and the number of service drops between transformers. Categorizing the homes into levels they labeled as very high current configuration, ordinary high current configuration, ordinary low current configuration, and very low current configuration combines the wiring class with an estimate of the distance from the wires to the home. Homes in neighborhoods served by buried wires have been considered a separate, low-exposure, group. Diagrams and a more detailed description are provided in this volume by Kaune (*7*).

Subsequent studies of childhood cancer have provided mixed support. A case–control study of leukemia in Rhode Island (*8*) was reported as negative based on an exposure classification system taken from that developed by Wertheimer and Leeper (*5*) for Denver. In addition to concerns with the applicability of the Denver system to Rhode Island and reliance on analyses of residences rather than persons, the different occupancy dates for cases and controls appear to have biased their measures of association toward the null, i.e., toward the absence of any association (*9*).

Tomenius (*10*) conducted a study in Stockholm in which homes were classified based on proximity to electrical constructions and magnetic field measurements at their front doors. Electrical constructions (specifically, above-ground power lines) were more common near case than control homes, and measured fields above 3 mG were more common among cases not near electrical constructions than comparable controls. Average magnetic fields were virtually identical for case and control homes. The positive association based on measured fields was restricted to nervous system cancers with an inverse association found for leukemia.

A second study in Denver (*11*) supported the hypothesis that children living in homes with higher wiring configurations or higher measured in-home magnetic

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Table 1. Comparison of results for measured magnetic fields and wiring configuration codes: residential characteristics and childhood cancer.

	Savitz et al. (*11*)			London et al. (*13*)		
Measure	Exposure level	OR	95% CI	Exposure level	OR	95% CI
Spot measurement of low power magnetic field (mG)	0–<0.65	1.0		0–0.32	1.0	
	0.65–<1.0	1.3	0.7–2.4	0.32–0.67	1.0	0.6–1.7
	1.0–<2.5	1.3	0.7–2.3	0.68–1.24	1.4	0.7–2.9
	2.5+	1.5	0.6–3.6	1.25+	1.2	0.5–2.8
24-hr measurement of magnetic field (mG)				<0.68	1.0	
				0.68–1.18	0.7	0.4–1.2
				1.19–2.67	0.9	0.5–1.7
				2.68+	1.5	0.7–3.3
Wire configuration code	Underground	1.0		Underground + Very low	1.0	
	Very low	1.6	0.8–3.1			
	Ordinary low	1.0	0.7–1.5	Ordinary low	0.9	0.5–1.7
	Ordinary high	1.5	0.9–2.4	Ordinary high	1.4	0.8–2.6
	Very high	2.2	0.9–5.2	Very high	2.2	1.1–4.3

fields under low power use were at increased risk of developing cancer, although the magnitude of association (odds ratios of 1.5–2.0) was lower than had been reported by Wertheimer and Leeper (odds ratios of 2.0–3.0) (Table 1). No association was found for electric fields or magnetic fields measured under high power use conditions. These results were not due to confounding by prenatal and childhood exposures reported by parents, but nonresponse and differential mobility of controls constitute important limitations in this study.

Myers et al. (*12*) recently provided results from a study conducted in the early 1980s in England. They interpreted their results as providing little evidence to support an association between childhood leukemia and residential electromagnetic field exposure, but their primary control group consisted of children with solid tissue tumors and diseases also potentially affected by this exposure. Elevated exposures were extremely rare, but there was modest evidence of increased risk with increased exposure.

The study completed most recently is methodologically the strongest and has a major bearing on the direction of future research. London et al. (*13*) recently reported the results of a case–control study of childhood leukemia and residential magnetic field exposure in Los Angeles County. The major improvements over Savitz et al. (*11*) consisted of the use of controls selected concurrently with case identification and a much more complete and extensive array of in-home magnetic field measurements. The results showed a clear association of wire codes with leukemia with more limited evidence of an association based on both spot measurements of magnetic fields and 24-hr measurements of magnetic fields (Table 1). In spite of their presumably greater accuracy as a reflection of long-term historical exposures, measurements taken over a 24-hr period failed to demonstrate a notably stronger association with disease than did spot measurements.

In addition to these studies of ambient background magnetic fields in homes, one study of childhood cancer reported on use of electrical appliances by the mother during pregnancy and by the child (*14*). Electric blanket use by the mother during pregnancy and by the child was associated with a modestly increased risk of developing childhood cancer, whereas heated water beds, bedside electric clocks, and other appliances used by the mother or child were not associated with increased risk.

There have been several studies of residential exposures and adult cancers. Wertheimer and Leeper (*6*) found modest positive associations between wiring codes and several types of cancer. Subsequent studies of residential exposures have been limited in quality of exposure assessment (*15*) or size (*16*) and generally are not supportive of such a link. Preston-Martin et al. (*17*) evaluated electric blanket use in relation to adult myelogenous leukemia and found no association.

Exposure Assessment Needs

If there is a causal relation between some aspect of electric or magnetic field exposure and cancer, there is no reason to believe that the exposure indicators used in past studies have captured it with precision. Modest associations in past studies may be masking a much more substantial effect that has been diluted by nondifferential misclassification, since our exposure indicators are only imperfect proxies for the potent exposure. This misclassification may operate on several levels, including the incorrect exposure metric (e.g., averages rather than peaks), failure to measure exposure comprehensively (e.g., ignoring sources other than the home), measuring exposure at the wrong period in the subject's life, as well as the familiar inability to measure precisely even in the desired places and times. Several strategies that would produce stronger measures of associations if such effects are actually present are available to improve exposure classification.

Models of Historical Exposures. All studies have relied on historical exposure reconstruction, including both the case–control studies and the cohort study (*15*). Instrumentation exists for relatively convenient acquisition of real-time individual exposure profiles over periods of several days (*7*). In spite of suggestions to collect individual-level data for prospective investigations (*18*), the rarity of the cancers that have been studied to date dictates that future studies are likely to continue to assess exposures retrospectively. Thus, the challenge faced by investigators is how to reconstruct an exposure history in the absence of direct measurements during the historical periods of interest.

One approach would be to develop predictive models of exposure in which the model inputs are amenable to historical ascertainment. The sources of electric and magnetic fields that we encounter in our daily lives are diverse and probably too complex to assess based solely on physics and engineering principles. It might be more fruitful to develop statistical equations that relate patterns of location and activity to measured fields. For example, detailed diaries could be maintained in parallel with real-time measurements of field strengths for a sizable and diverse population of children or adults outside the context of a specific case–control study. Statistical models to estimate various field parameters of interest then could be developed based on locations and activities. The predictors in those models would have to be amenable to historical assessment in order to be useful, recognizing that in reality some would be (e.g., use of electric blankets) and some would not (e.g., how close the child sat to the television).

Such an approach would be enhanced by methods for reconstructing historical exposures within the most important (i.e., frequently occupied) environments. Wire configuration codes were intended as historically stable markers of in-home exposures, because power lines are rarely modified (*5*). Although the wire codes have been demonstrated to be associated with current magnetic fields in homes, the strength of prediction is quite limited. The structure of the original Wertheimer and Leeper (*5,6*) wire code was developed intuitively. Further examination of whether there are better ways to integrate information on observable characteristics of the wiring using physics and engineering principles should be undertaken, and empirical estimation [such as that developed by Kaune et al. (*19*)] offers promise for making more accurate inferences from the historically stable electrical constructions.

Exposure sources other than the ambient levels found in homes also should be considered. There is no information on whether some variant of a wiring configuration code could be developed for schools or commercial buildings where substantial periods of time are spent. Appliance use certainly has the potential to be incorporated into a comprehensive historical exposure assessment.

Wire Codes versus Measurements. The report by London et al. (*13*) of a clear association of childhood leukemia with wire codes and a weaker association with measured magnetic fields, even taken over a 24-hr period, highlights the need to better understand what aspects of past and present exposure are reflected by each (*7*). The logistical considerations are as follows: *a*) better response for wire codes (passive on the part of the respondent) than for in-home measurements (requiring the respondent's cooperation), which would increase study size and diminish the potential for bias; *b*) greater expense for in-home measurements due to scheduling inefficiencies and equipment; and *c*) less need for engineering expertise to use a meter than to develop a wire coding methodology.

The key unanswered question remains the validity of the different strategies as indicators of historical exposure. Prospective studies are needed and would be simple to conduct. A panel of homes, without concern for the health status of their occupants, could be recruited for long-term evaluation with a battery of measurements and wiring characteristics. Periodic repeat measurements would monitor changes over time. This should be coupled with individual monitoring of occupants of selected homes so that the residential information could be understood in the context of other exposure sources. The effect of differing patterns of room use over time, modification in the use of rooms and their physical arrangement, and changes due to shifts in the occupants could be assessed empirically for their bearing on historical exposure reconstruction. If predictable relations were found, they could be queried and incorporated into exposure assessment protocols. On the other hand, even if such sources of inaccuracy could not be remedied, at least they could be quantified and considered in interpretation of results. The necessary database would be rather tedious to initiate and maintain, but it would be of great value with the passage of time.

Alternative Exposure Parameters and Sources. For a number of practical and theoretical reasons, interest has focused on long-term average magnetic fields in homes. Because magnetic fields are largely unperturbed by trees, building materials, etc., the power lines have a systematic relation to in-home fields. Electric fields, equally ubiquitous, have no marker analogous to wire codes that would allow their effects to be examined. Empirical approaches to examining exposure sources might yield some historically applicable indicators of electric field exposure, although this is unlikely based on a knowledge of exposure sources and past epidemiologic study results (*11,19*).

The specific attributes of the magnetic fields predicted by wiring codes also remain mysterious (*7*). The relation of wire codes to peaks, transients, various percentiles, time above or below postulated thresholds, etc. could be examined to assist in interpretation. That ultimately may suggest modifications to wire codes to serve as surrogates for different types of indices. Guidance for laboratory investigators could be much more specific if the fields predicted by wire codes were better understood.

Finally, additional examination of appliance-based exposures is warranted. The effectiveness of asking about the use of such devices seems straightforward, but the validity of self-report on use of key appliances, including patterns of use (e.g., proximity to television set), warrants examination. The yield, in terms of refinements in exposure classification, from more sophisticated inquiries should be evaluated: Is it worthwhile to ask the brand of video display terminal or the setting on which electric blankets are used? It seems likely that appliances that do not contribute to average magnetic field still may contribute substantially to other indices, such as peaks or time above a given level (e.g., hair dryers). Such questions could be examined as part of an effort to develop statistical models of exposure starting with an effort to completely reconstruct sources of electric and magnetic fields.

Health End Points

Studies of both childhood and adult cancers have followed traditional approaches to disease classification. For childhood cancer, in particular, rarity of the disease has led to broader groupings than might be desirable. These groupings may dilute any effects of electric and magnetic field exposures on cancer subtypes. In some instances, all childhood cancers have been grouped together, although most investigators have also examined subtypes such as acute lymphocytic leukemia, lymphomas, brain tumors, etc. More attention should be paid to examining more refined disease subtypes. For example, among leukemias there is some suggestion that different cytogenetic subtypes have different etiologies (*20*). This implication encourages the evaluation of the role of electric and magnetic fields for those subtypes. Histologic categories of brain cancer recently have been shown to have markedly different associations with electrical occupations (*21*) and should be examined with respect to residential exposures as well. The practical challenge is assembling study populations that are large enough to have sufficient precision in examining subgroups. This also applies to the myriad forms of childhood cancer that are far too rare to consider in individual studies (e.g., osteosarcoma, Wilms' tumor). Meta-analysis using data from several completed studies would be one possible approach.

Although occupational literature suggests that electric and magnetic fields may be related to leukemia and brain cancer, these implications have not been pursued extensively in studies of residential exposures. There have been some studies focused on residential magnetic field exposure and adult leukemia (*16,22*), and some studies of all forms of cancer (*6,15*). Although the results of residential studies have been largely negative, this avenue ought not be abandoned for several reasons. There is no biological reason to believe that childhood cancers are uniquely susceptible to magnetic fields. Given the rarity of childhood cancers and the consequent difficulty in conducting research, adult cancers are also worthy of concern. The continued support for a role of occupational exposures in the etiology of leukemia, especially acute myeloid leukemia; brain cancer; and, to a lesser degree, melanoma and lymphoma would encourage closer examination of residential exposures. Studies of residential exposure and adult brain cancer would be warranted by the evidence but have not yet been undertaken.

When biological understanding of the effects of electric and magnetic fields has progressed sufficiently, early, more highly prevalent disease indicators (biomarkers) of electric and magnetic field exposure may be identified. If such outcomes were sufficiently frequent, then prospective studies in which individual subjects would be monitored over days, or even weeks, for the development of the end point of interest could be developed, or banks of biological specimens could be exploited for nested case–control studies. Even if the marker were simply an integrator of exposure rather than a marker of a step in disease development, it potentially would be of value in identifying the most biologically potent aspect of exposure and in assisting in the design of studies of the more clinically significant end points. Some biological correlate of melatonin could serve as such a marker if more persuasive evidence linking the exposures and disease of interest to this pathway were to accrue, but a number of logistical issues would need to be overcome (*23*). Unfortunately, there are no other obvious candidates on the horizon, because the classic markers of genotoxicity (chromosomal aberrations, sister chromatid exchange, micronuclei) would not be expected to be useful in spite of some evidence for increased micronuclei formation among mice exposed to electric fields (*24*).

Considerations in Study Design

Several features of the past studies of residential magnetic field exposure and cancer have not been examined adequately as a potential basis for biased results. This includes several potential positive biases (which would produce spuriously elevated associations) and negative biases (which would produce spuriously reduced associations).

Control Selection and Wire Codes. The process of control selection in childhood cancer studies raises a number of concerns regarding the extent to which an unbiased sample from the study base has been attained. Several different methods have been used, including birth certificate controls (*5,8*), population register controls (*10*), and random digit dialing controls (*11,13*). Success in obtaining controls who are a random sample of the population from which the cases arose is difficult to demonstrate, given how little is known about the important determinants of exposure. In the study by Savitz et al. (*11*), for example, differential mobility of cases and controls may have introduced bias, but the presence or absence of such bias could not be demonstrated directly. In contrast, London et al. (*13*) obtained controls concurrently with case identification and obtained similar patterns of association, which suggests that differential mobility does not account for the pattern of results found by Savitz et al. (*11*).

Methodological evaluation of control selection for studies of residential magnetic field exposure should be undertaken. Because of our limited knowledge of the causes of childhood cancer as well as leukemia and brain cancer in adults, the exploration should extend beyond known risk factors to include: *a*) examination of a number of household characteristics in relation to magnetic fields, including socioeconomic characteristics, availability of a telephone, household composition (number and ages of children, etc.), patterns of residential movement and duration of occupancy, age of housing, and proclivity to participate in surveys; *b*) revaluation of the recently completed studies that used random digit dialing to assess the extent to which controls represented the general community and, particularly, households with children; and *c*) examination of alternative control selection strategies such as telephone directories, school records, and door-to-door canvassing. The costs of various alternatives and the yield of information should be examined.

Nonresponse and incomplete coverage are always possible sources of bias worthy of consideration. Although random digit dialing is a well-accepted technique, when the screening nonresponse and interview refusal rates are combined the losses can be rather severe (*25*). However, one of the advantages of using wiring codes as an exposure marker is that identifying an eligible address is sufficient to obtain the code; the home can be coded even if the respondent ultimately declines to be interviewed or allow in-home field measurements. The critical unknown relation is between nonresponse and wire code, and it is that uncertainty that makes evaluation of selection bias an important avenue to pursue.

A second product from a thorough examination of correlates of residential magnetic field exposures in the community would be improved guidance regarding possible confounders. Our knowledge of the etiology of childhood cancers in particular is quite limited. One approach to exploring possible confounders is to learn more about the characteristics of persons who live in homes classified as having elevated exposures. These characteristics would not, of course, necessarily be confounders, but they would satisfy at least one of the necessary criteria and could then be evaluated for their independent association with cancer risk.

Given the prominence of wire codes as a marker of cancer risk and the severely limited understanding of their implications, a broader evaluation of the sociology and geography of wire codes seems to be essential to identify the most valid approach to control selection and confounding. Understanding the patterns of wire codes within the community in broad and comprehensive terms of the spatial distribution of wires and wire codes, demographic and behavioral aspects of those who choose to live in homes of varying wire codes, and a comprehensive evaluation of empirical correlates of wire codes would serve several important research needs. Such knowledge would address a number of key methodological concerns simultaneously: the likelihood of selection bias in past case–control studies due to the constitution of the control group; suitable methods for selection of controls in future case–control studies; the likelihood of confounding by other exposures associated with wire codes; and the possibility that the impact of wire code on cancer risk is mediated through something other than the average magnetic field in the home.

Timing of Exposure. Timing of exposure, based either on when it occurs during the day or when it occurs during the individual's life, has received little attention. The possibility of an effect on melatonin synthesis suggests an emphasis on nighttime exposures, which is implicit in residential studies and would be especially applicable to studies of electric blankets and heated water beds [although it is questionable whether the pineal gland is exposed from such sources (*26*)]. No studies of childhood cancer have examined adequately the temporal relation between exposure and disease by hypothesizing and testing expected induction and latent periods. Clearly, the temporal sequence of events leading to cancer is briefer than the corresponding multidecade process in adults.

There has been some cursory consideration of this issue in several studies (*5,11*), but none have obtained the desired lifetime residential exposure history to allow comprehensive evaluation of all potentially important time windows. Given our ignorance of the temporal course of disease induction, all exposure preceding disease is of potential interest, but presumably, some etiologically irrelevant exposures have been included in past studies and obscured any etiologic effects (*27*). The only well-established environmental cause of childhood cancer, exposure to ionizing radiation, has been shown to operate *in utero* (*28*), although the mechanisms of this type of exposure would be quite different than the possible effect of magnetic fields. Nonetheless, exposures *in utero* constitute one period of particular interest.

Logistically, assembling such lifetime histories is challenging and requires a residentially stable population. Urban areas with highly mobile populations such as Los Angeles or Denver are not good choices on this criterion, and many of the formerly occupied homes are outside the study region. On the other hand, without changes in residence, isolation of any effects of exposure in specified periods of life is impossible. Passive exposure assessment procedures (e.g., wire configuration codes) are more amenable to gathering a complete exposure history than procedures requiring respondent cooperation (e.g., in-home measurements). The presumption that any effects of magnetic fields only operate late in the etiologic process should be scrutinized since it seems to be based largely on the inability of such fields to cause mutations.

Ecologic Studies. Studies of disease patterns in populations over time or space, in which the group's magnetic field exposure is related to its cancer incidence, should be considered in spite of the well-known challenges posed by the ecologic fallacy (*29*) and from exposure misclassification (*30*). A principal motivation is to respond to critics who argue that secular changes in the use of electric power have been dramatic through this century and have produced a marked increase in electric and magnetic field exposure that has not yielded a corresponding increase in the cancers of concern (*31*). Obviously, this scenario would apply only if magnetic fields were a very strong contributor to cancer risk and if magnetic fields increased as electric power use increased, but such analyses still could place some upper bound on the magnitude of association.

This possibility could be examined empirically by isolating each of the assumptions and consequences. The argument that exposures have risen proportionately to the use of electric power has not been tested, and theoretical arguments against such a rise include the increasing suburbanization of America (with larger yards and greater distance from power lines), greater use of underground lines, higher voltages on lines, and more electricity-efficient appliances (such as microwave ovens and digital clocks). Wertheimer and Leeper's (*9*) examination of data from the Rhode Island study suggested that more recently occupied homes (which tended to be more suburban) had lower wire configuration codes on average.

Although historical measurements of individual exposures in the past are not available, the pattern of wire codes over time could be easily examined in several ways. Data on wiring configurations from the earliest studies conducted in the late 1970s could be compared to those conducted in the present, yielding a 10- to 15-year contrast. The housing stock at different historical periods could be estimated based on county tax assessment records to simulate the mix of wire codes in different historical periods. Even within completed studies, the dates of occupancy could be examined in relation to the wire codes of the homes.

Historical data on the cancers of interest are also necessary to conduct a study of time trends. A few cancer registries, such as the one in Connecticut, go back far enough in time. Mortality from childhood cancers (especially leukemias) has been so markedly changed by effective treatments that mortality data do not adequately reflect incidence. Additional challenges to making valid comparisons across long spans of time are posed by improving quality of diagnosis and the techniques used to classify cancers in different eras.

A study of geographic variation in residential exposure is more promising because potential confounders are likely to vary less markedly across the United States at the present time than over lengthy periods of interest. If there are systematic spatial differences in average exposure based on region, urban–rural differences, etc., then ecologic studies could examine efficiently the corresponding patterns of cancer incidence and mortality. For example, high current configurations appear to be more common in Los Angeles than Denver (*11,13*). Perhaps in large midwestern and northeastern cities, the prevalence of homes with such configurations may be greater still. Although limited to detecting gross differences, assessment of geographic patterns in mortality could yield some information if marked exposure gradients are present. The usual considerations in assessing the value of ecological studies apply: the opportunity to study wide exposure variation and a very different set of methodological concerns relative to those that apply to studies of individuals (*32*) is balanced against the effort required to conduct the research. The effort required to characterize spatial and temporal variation in exposure accurately is not known at present; but if not unduly demanding, it would at least produce a systematic evaluation of the argument that secular trends in exposure demonstrate the implausibility of an etiologic association with cancer.

An additional benefit of such an evaluation would be its use in pinpointing areas in which research might be most profitably conducted. Limited numbers of homes in the highest exposure groups have decreased the precision of all past studies, so areas with greater prevalence of higher magnetic field exposure would be most favorable for research.

Research Priorities on Residential Exposures

The preceding sections have sought to define comprehensively the issues deserving consideration and empirical research in order to advance our understanding of residential magnetic field exposures and cancer. Ideally, the reader should have sufficient information to reach independent conclusions regarding priorities. However, suggestions for the most pressing research needs are offered.

Two types of methodologic studies are needed to better interpret past studies and design future ones: assessment of individual magnetic field exposure sources and patterns and determination of correlates of wire code in the community. Either or both of these might be embedded into an ongoing study or conducted independently.

Evaluation of exposure sources through personal monitors and diaries combined with wire codes and home measurements would simultaneously define the exposure sources most worthy of study, address the relation between wire code and personal exposure, and allow examination of different exposure metrics. Past studies relying on only one exposure source (e.g., wire codes, electric blankets) could be reinterpreted and future studies could focus on the most applicable exposures. Possible efforts to reduce exposures would also benefit from knowledge of how exposures are actually incurred.

Knowing the patterns of wire codes in the community is essential to evaluating theories of confounding, selection bias, and alternative causal pathways. Confounding would occur if wire codes were associated with an independent cause of cancer; selection bias would occur if study participants are unrepresentative of the target population; and an alternative causal pathway would operate if wire codes do not cause cancer through the resulting magnetic field exposure. Consideration of the sociological, geographical, and behavioral correlates of wire codes would provide empirical guidance to those who interpret studies that evaluate the possibility of bias as well as those who design future studies. It may seem more efficient to measure all possible confounders and adjust for them or to choose directly the correct control group, but without a clearer understanding of the likelihood of error, the inevitable design trade-offs cannot be made intelligently. Control groups, for example, may be selected in a limited number of ways, with random digit dialing the most popular for logistical reasons. The relationships among telephone access, social class, willingness to participate in surveys, and wire codes would be substantially valuable in determining whether some more onerus method of control selection is truly needed or whether studies need to be conducted in locales in which population registers are available. Without the pertinent background information on vulnerability to selection bias, selection of a single, appropriate, and credible control group is virtually impossible.

Occupational Exposure

Synopsis of Evidence

There has been a large number of studies in which job titles presumed to be indicative of above-background exposure to electric and magnetic fields have been examined in relation to cancer. Most commonly, such studies have focused on leukemia and brain cancer. The evidence has been reviewed in several publications (*1,2,33–35*). Most reviewers share the conclusion that these reports generally support an association between work in electrical occupations and the risk of leukemia, especially acute myeloid leukemia, and brain cancer. Magnitudes of association vary greatly from null to sizable increases, but elevations in risk on the order of 1.5 to 2.0 are commonly reported, especially in proportionate mortality, incidence, and case–control studies. Most cohort studies have not found the associations to exist to the same degree. Given the lack of sophistication in exposure assignment, the degree of consistency across diverse populations is notable. Other cancers, such as melanoma (*36,37*), lymphoma (*38*), and male breast cancer (*39–41*) have been implicated, but with less replication.

The structure of these studies has included registry-based examinations of proportionate mortality or incidence, registry- and community-based case–control studies, and historical cohort studies among electrical workers. Starting with Milham's (*42*) report, all have used job title as the exposure surrogate with some refinements in terms of more sophisticated classification systems (*43*) but largely relying on an intuitively developed listing of jobs thought to entail elevated electric and magnetic fields (e.g., electrician, lineman, television repairman).

A separate avenue of research on occupational exposures and cancer is that of paternal influences on childhood cancer risk. Spitz and Johnson (*44*) found that children who died from neuroblastoma more often had fathers who were employed in occupations thought to have electromagnetic field exposures than controls did. The increased risk was concentrated among electronics workers. These results were replicated to some extent by Wilkins and Hundley (*45*) in a similarly designed case–control study of neuroblastoma, but Bunin et al. (*46*) reported an absence of increased risk for neuroblastoma in relation to paternal exposure to electromagnetic fields. The mechanism for such an effect is tenuous, given that the agent is incapable of causing mutations in sperm, but perhaps some other mechanism of interfering with sperm production is applicable.

Exposure Assessment Needs

Evaluation of Nonutility Populations. Among electrical workers, electric utility workers have been most actively considered. While such studies are in progress, there is a need to identify additional groups of workers who are suitable for study. Studying other populations would provide an assessment of the replicability of the evidence from utility workers. More important, the actual exposure circumstances in terms of field frequencies and temporal patterns vary markedly among electrical workers, and if any such exposures are carcinogenic, there may be some more and some less potent forms of exposure among the different groups of workers. The variability in exposure circumstances, both quantitatively and qualitatively, is much greater in the workplace than in the home. This should produce more informative studies in the occupational setting if those exposures can be characterized adequately.

In the past, the interest has been in relatively rare cancers (leukemia and brain cancer), and the examined populations had to be sizable and there had to be a mechanism for identifying them (company or union records, for example). Starting with a roster of candidate worker groups, exposure measurement surveys would be essential to indicate that they truly have above-background exposures and to characterize the general patterns of that exposure. Candidate populations widely discussed include aluminum workers, electric railroad workers, arc welders, and other workers who work near electric motors.

Community-based studies may also address occupational exposures using some explicit or implicit job-exposure matrix that links job title to exposure. This is the basis of virtually all of the existing literature based on death certificates or cancer registries. It seems that the inability to characterize exposures generically across widely divergent job titles and industries gives these studies limited potential to advance the literature. Although it would be useful if widespread electric and magnetic field exposure surveys enabled us to characterize adequately exposures associated with specific job titles and industries, the variation within those groupings is likely to limit the value of broad job titles. In contrast, within an industry, the level of refinement can be much greater.

Improved Historical Markers. Because leukemia and brain cancer are so rare, it is not feasible to undertake prospective cohort studies for either, although future interest in more common cancers such as prostate cancer or female breast cancer would introduce that possibility. Nonetheless, most future research will continue to rely on historical markers of exposure, typically job titles and other documented information on work activities and locations. There is a need to validate such markers through present measurements and by other indirect means. There is also a need for imaginative approaches to reconstructing the historical exposures of interest, including simulation of past work environments and practices where possible. In a recent study of workers who used video display terminals, for example, exposures associated with outdated equipment were estimated by retrieving some of the old equipment for measurements (*47*).

In addition to evaluating the adequacy of the surrogate marker in the future, it would be useful to assess just what exposures the surrogate marker predicts. Preliminary examination of job titles of electric utility workers (*48*) suggests that jobs thought to be exposed have a stronger gradient for magnetic than electric fields. Similarly, one might ask about the distinctions based on job title for different exposure indices (e.g., mean, median, peak) or for different frequencies. Future epidemiologic and laboratory research would benefit from obtaining more specific suggestions about the form of exposure reflected from job titles.

A more ambitious advancement would require incorporation of nonoccupational exposure sources into occupational studies. This is more feasible than the converse, extending residential studies to incorporate workplace exposures, since validated markers of nonoccupational exposure are available. Specifically, cohort mortality studies could be followed up with nested case–control studies that include interviews with living subjects or next of kin for decedents in which nonoccupational exposures would be estimated. Identification of the residences in which they had lived could be coupled with wire coding or measurements of those homes. Possible use of appliances such as electric blankets and heated water beds could be queried and probably could be accurately reported by a surviving spouse or child. Qualitative and probably even quantitative indices of exposure that combine diverse sources of exposure could then be developed and analyzed in relation to cancer risk. If some measure of total dose is the important one, such combined indices would be markedly better at predicting cancer risk than either component alone, since a sizable contribution to total dose comes from each source (*17,48*).

Health Outcomes

As seen in residential exposure, there is potential value in examining more specific subtypes of cancer. This is predicated on the possibility that more specific forms of cancer, defined by histology and cytogenetics, may show stronger relations to electric and magnetic field exposure. The generally stronger associations found for acute myeloid leukemia compared to other leukemias (*35*) and the recent evidence that astrocytomas show markedly stronger associations with electrical work than other forms of brain cancer (*21*) suggest that such efforts could yield important information.

On the other hand; there is no clear biological rationale for focusing on leukemia and brain cancer only, and as noted above, associations with melanoma, lymphoma, and male breast cancer have also been reported. We should retain the ability to discover that some other type of cancer is strongly related to exposure or to confirm or refute the reports of such associations in other studies. In general, studies that adequately can address many forms of cancer, such as historical cohort studies or case–control studies used with a case group of all cancers, are preferred to those that cannot.

In parallel with the suggestion for residential studies, markers of exposure or disease that are prevalent enough to be studied prospectively would be highly desirable. Current technology permits exposure assessment over periods as long as several weeks, but without some end point that can be observed in a short time frame and of adequate prevalence, such measurements can only serve to validate such exposure proxies as job title.

Study Design

Consideration of Other Exposures. Because of substantial contributions from the residence and appliance use (which may have substantial between-subject variability), it is understood that the workplace is not the only or even the dominant source of exposure (*49*). Logistical constraints make it difficult to integrate exposures across diverse sources, so further examination of the consequences of ignoring nonoccupational sources should be more carefully considered. Exposure surveys suggest the absence of any association between workplace and nonworkplace exposures among utility workers (*48,49*), but the consequences for studies of workplace exposures are not clear. There may also be reason to believe that some highly exposed occupational groups would tend to have exposures in their hobbies, such as operating radios or other electrical equipment. Considering a number of possible relations between work and nonwork exposures for their impact on observed dose–response gradients would assist in the interpretation of past studies and planning of future studies.

Confounding has been of particular interest in this literature, because a job title virtually always suggests exposures in addition to the electric and magnetic field exposure of interest. Many groups of electrical workers have the potential for occupational exposure to solvents, polychlorinated biphenyls (PCBs), soldering or welding fumes, etc. The impact of many of these agents on cancer risk is poorly understood, but future studies should examine them as effectively as possible. Nonetheless, hypothetical calculations for the magnitude of confounding by a carcinogen as potent as cigarette smoking (*50*) suggest that extreme and perhaps implausible scenarios are required to invoke such confounding as a critical threat to the validity of these studies.

An efficient approach to examining cancers that have not been thoroughly considered, such as lymphoma and melanoma, would be to pool results from the numerous surveys and cohort studies using meta-analysis. By examining a wide array of cancer types in that manner, patterns may emerge that were not previously appreciated. Even leukemia and brain cancer might be better understood through a more quantitative integration of the literature.

Effect-Modification by Timing and Other Agents. A critical deficiency in nearly all of the past studies that have relied on registry data is a failure to consider temporal aspects of exposure and disease. The extreme version is the death certificate-based study (*42,51*), in which there is no information whatsoever on the duration of employment in the listed job, when work in the job ceased, or what other jobs were held. Presumably, if there is an etiologic relation, like all others identified to date, there is some specificity for the induction and latent periods. Restricting the windows of exposure to the pertinent ones would enhance any causal associations. The assumption that electric and magnetic fields act at late stages should be addressed empirically by assessing cancer risk in relation to exposures in a recent time window. More generally, a flexible, trial and error approach to specifying the potential windows of importance should be adopted (*27*), especially when considering an agent for which the underlying biological processes are so poorly understood.

Finally, the possibility that the effects of electric and magnetic fields are enhanced by exposure to other agents should be evaluated. If such exposures are thought to act in concert with genotoxic agents, then one would expect some effect modification to be discernible. As noted above, there are a number of potentially carcinogenic agents such as solvents and PCBs thought to be prevalent among electrical workers, so the ability of such exposure to potentiate the effect of electric and magnetic fields could be examined. If future study designs permit consideration of nonoccupational exposures, then cigarette smoking would be of great interest as a potential effect modifier.

Research Priorities in Studies of Occupational Exposure

Among the suggestions offered for extending knowledge regarding occupational exposure to electric and magnetic fields and cancer, two avenues are the highest priorities. First, exposure patterns of groups of workers potentially amenable to epidemiologic study need to be assessed. Identification of groups with above-background exposure is an absolute requirement, but the likely diversity of exposure forms and patterns (frequencies, temporal patterns of exposure, historical exposures) also should be understood in order for the epidemiologic studies to begin to clarify the circumstances in which adverse effects are and are not observed.

Second, following identification of suitable groups for epidemiologic study, more empirical information on occupational groups with a diversity of forms and patterns of electric and magnetic field exposure is needed. Traditional cohort or nested case–control studies within industries are most likely to be informative. By studying workers with elevated but distinct exposure patterns, the consistency of any increased risk of leukemia, brain cancer, or other cancers can be assessed and there is the possibility of identifying a group with a more potent exposure pattern.

Conclusions

The strategies outlined above can be divided into three groups by considering the effect the methodological deficiencies would have on the estimated measures of effect (i.e., the risk ratio or odds ratio). Improvements typically have one of the following goals: *a*) to reduce bias toward the null (false negative results), enhancing the magnitude of association if an underlying etiologic effect of electric and magnetic fields on cancer truly exists; *b*) to reduce bias away from the null (false positive results), diminishing positive associations reported in past literature if they are actually a result of errors in study design or execution; and *c*) to enhance precision of study results.

The principal source of potential bias toward the null is nondifferential exposure misclassification. Such nondifferential misclassification applies to all of the sources of discrepancy between operational measures of exposure in a given study (e.g., job title, wire code of residence) and the precise biological measure of dose that is etiologically effective (e.g., time-integrated total magnetic field, time above 2 mG). Any study design strategy that better approximates the biologically relevant dose (typically identified through trial and error) will enhance the magnitude of association if an etiologic effect is present. Better wire codes, more precise job titles, incorporation of other sources of exposure, consideration of different exposure parameters, and examination of varying time windows of exposure all have that intended effect. The search for effect modifiers can be viewed in this light, with the group in which the effect of electric and magnetic field is enhanced reflecting a stronger association with cancer. Also, the effort to define more specific subgroups of cancer more strongly associated with exposure fits into this category. If reducing misclassification increases the measures of association, then the likelihood that there is a true etiologic effect present is enhanced. Conversely, extensive unsuccessful efforts to identify a stronger relation could be interpreted as evidence against a causal effect, although it would not be clear when the search should be ended.

Potential sources of bias away from the null are less obvious in past studies of electric and magnetic fields and cancer. In the community-based studies, selection bias in the constitution of the control groups is an important consideration. The constitution of the control groups is challengeable (generally based on random digit dialing), as well as the potential bias due to nonresponse. For this to produce bias away from the null, a particular pattern (e.g., missing higher exposure controls) would have to be invoked. In both occupational and residential studies, the potential for unmeasured positive confounders should continue to be examined. Specific, testable candidates for sources of bias away from the null are needed to make progress in this area.

Finally, some of the above strategies are intended primarily to enhance precision. Identification of communities or workforces with a higher prevalence of elevated electric and magnetic field exposure should yield more precise estimates of effect. Meta-analyses of completed studies have the potential to yield increased precision in estimates of dose–response gradients. Finally, study of early disease markers could provide a much more common outcome than cancer, with consequently greater precision.

The strategies suggested in this paper are intended to open research avenues. Although some of the more obvious studies have been done or are in progress, there are some other pathways that would yield new insights regardless of the results obtained.

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