Annu. Rev. Public Health. 1998. 19:101–23

ENVIRONMENTAL RISK FACTORS AND FEMALE BREAST CANCER

Francine Laden[1, 2] *and David J. Hunter*[1, 2, 3]
[1]Department of Epidemiology, Harvard School of Public Health, [2]Channing Laboratory, Department of Medicine, Harvard Medical School and Brigham and Women's Hospital, [3]Harvard Center for Cancer Prevention, Boston, Massachusetts 02115; e-mail: francine.laden@channing.harvard.edu; david.hunter@channing.harvard.edu

KEY WORDS: organochlorine, EMF, passive smoking, ionizing radiation, geographic variation, clusters, breast cancer, environment

ABSTRACT

The increasing incidence of breast cancer in the United States and the international variation in risk have led to speculation that environmental risk factors are an important cause of breast cancer. We review the epidemiologic evidence on the breast cancer risk associated with ambient environmental exposures experienced passively by the US population, and discuss the difficulties associated with measurement of specific exposures in environmental studies. We review geographic variation of breast cancer rates in the United States, and exposure to organochlorines, ionizing and electromagnetic radiation, and passive smoking. Results are inconclusive but do not support a major role of environmental risk factors in the etiology of breast cancer.

INTRODUCTION

Breast cancer incidence rates in the United States have increased by 1% per year since 1940 (46). Rates in the United States are among the highest in the world, and rates in Western industrialized countries are as much as fivefold higher than rates in Africa and Asia (22, 54). Furthermore, daughters of women who migrate from low-incidence to high-incidence countries acquire the breast cancer risk prevailing in the new country (16), suggesting that aspects of lifestyle or the environment are the major determinants of breast cancer. Studies of atomic bomb survivors have shown that ionizing radiation, an environmental exposure, is a risk factor for breast cancer (102). Because it is uncertain how

0163-7525/98/0510-0101$08.00

much of the change in breast cancer risk over time and the international variation in risk can be explained by established reproductive and other risk factors, there has been much speculation that environmental exposures other than radiation are important causes of breast cancer (26, 120).

We review the evidence on the breast cancer risk associated with ambient environmental exposures relevant to the US population. It is unfortunate that there is confusion as to what constitutes an "environmental" exposure. Epidemiologists often label as "environmental" any risk factor that is not genetic, including diet, body size, exogenous estrogen use, reproductive factors, and medical treatments. Using this definition most breast cancer is thought to be due to the "environment," as only a small proportion is due to inherited mutations in breast cancer susceptibility genes. The general public, however, often interprets this as evidence that much of breast cancer is due to "environmental" pollution. In this review, we restrict the definition of environmental exposures to those which a person experiences passively, due to pollution or other characteristics of the outside world. We discuss geographic variation of breast cancer rates in the United States, exposure to organochlorines, exposure to ionizing and nonionizing (electromagnetic fields) radiation, and passive smoking. We present avoidable personal exposures and occupational exposures only when they are relevant to issues of environmental exposures in the general population. These environmental exposures have been selected as potential breast cancer risk factors based on biological hypotheses that we discuss in brief before presenting the epidemiological evidence.

An often quoted estimate is that only 30% of breast cancer cases are explained by known risk factors (25, 94a), suggesting that major risk factors remain to be discovered. However, a recent study of population-attributable risks in a nationwide survey estimated that at least 45% to 55% of breast cancer cases in the United States may be explained by later age at first birth, nulliparity, family history of breast cancer, higher socioeconomic status, earlier age at menarche, and prior benign breast disease (69). Other statistical models appear to explain an even higher proportion of breast cancer on the basis of known risk factors (21). Although it is difficult to determine precisely how much of the secular trend of increasing breast cancer rates is due to the changing prevalence of known risk factors, this proportion is almost certainly substantial, limiting the potential contribution of yet to be determined environmental exposures.

In Table 1, we present some selected events in the "modernization" and urbanization of the United States that have been hypothesized to be relevant to increasing breast cancer rates, along with the incidence rates from the Connecticut Cancer Registry, the most complete longitudinal incidence data in the United States. For descriptive purposes, we have also included information on time trends of some of the accepted breast cancer risk factors to illustrate their change over time.

Table 1 Selected "environmental" events in the United States, prevalence of key breast cancer risk factors, and breast cancer incidence in Connecticut by decade

	"Environmental" events	Breast cancer risk factors	Incidence[a]
1870	Light bulbs invented (1879)[b]	Age menarche: 14.8 years[c]	
1900	Model T invented (1908)[d]	Age menarche: 14 years[c]	
	US population 40% urban[e]	33% nullip; 86% afb <30[f]	
	8% homes electrified[b]		
1910	Home appliances invented[b]	36% nullip; 86% afb <30[f]	
1920	PCBs introduced (1929)[g]	28% nullip; 86% afb <30[f]	
	US population 51% urban[e]	Women start smoking	
1930	80% urban homes electrified[b]	26% nullip; 89% afb <30[f]	
	11% rural homes electrified[b]		
1940	DDT introduced (1943)[g]	30% nullip; 80% afb <30[f]	56.6
	Natl. Highway Network (1947)[d]		
	US population 57% urban[e]		
	25% women in labor force[h]		
	Suburbanization[d]		
1950	Peak production DDT[g]	21% nullip; 81% afb <30[f]	63.4
	Commercial nuclear power[b]	Age menarche: 12.8 years[c]	
	80% rural homes electrified[b]		
1960	37% women in labor force[h]	Oral contraceptives	68.8
	US population 70% urban[e]	Postmenopausal hormones	
		13% nullip; 91% afb <30[f]	
1970	Peak production PCBs[g]	10% nullip; 93% afb <30[f]	80.4
	DDT banned (1972)[g]		
	PCB production ceased (1977)[g]		
1980	US population 73.7% urban[e]		91.2
1990	57% women in labor force[h]		116.5[i]
	US population 75% urban[e]		

[a]Average annual age-adjusted (1970 US Standard) incidence rates per 100,000 population, Connecticut; Heston et al 1986 (48).
[b]US Department of Energy 1996 (108).
[c]Average age at menarche for US population, Wyshak et al 1982 (124).
[d]Chudacoff et al 1981 (19).
[e]US Bureau of the Census: 1900, 1920, 1940 (104); 1960 (105); 1980 (106); 1990 (107).
[f]Connecticut women, 40 years old on average at midpoint of decade; nullip = nulliparous, afb = percentage age at first birth <30 years among parous women; Hahn & Moolgavkar 1989 (44).
[g]Ahlborg et al 1995 (3).
[h]Percentage of women >age 14; Roberts 1993 (88).
[i]Kosary et al 1995 (55).

ISSUES IN ENVIRONMENTAL EPIDEMIOLOGY OF ANY CHRONIC DISEASE

There are many methodologic issues that make environmental epidemiology of chronic diseases especially challenging. These mainly center around problems of exposure measurement. First, in most circumstances, pollutants are

ubiquitous and occur in the ambient environment at very low levels. Therefore, exposure is hard to measure accurately, and it may be difficult to identify an unexposed population. An exception is the evaluation of major releases of contaminants due to an event such as an industrial accident or the atomic bomb. Low-level exposures are also often associated with small hypothesized relative risks that are difficult to assess statistically in small studies.

Second, because environmental exposures are indirect and are experienced passively, it is difficult to quantify the dose to an individual. Individuals may not know whether and to what extent they were exposed to a given pollutant, so direct questions cannot be used for assessment. If the exposure is still present, personal monitors can be used to measure exposure; however, this is often expensive and time consuming. Researchers can evaluate proxies of exposure, current and past, such as place and duration of residence, job title, and assessment of other activities. The level of exposure is quantified with present-day "area" measurements or historical records. Indirect exposure assessment, grouping of job titles, and "area" measurements can lead to substantial misclassification of individual exposures because the actual exposure to the individual may vary due to her experiences and activities. If this error is independent of disease status (nondifferential) then the relative risks for binary exposures are attenuated, increasing the difficulty of detecting a small real effect. In addition, assessment of dose response will be compromised.

Biomarker studies are one approach to avoid the problems of individual exposure assessment. Concentrations of a pollutant or its metabolites in biological media (often tissues or blood) measure internal dose, and if the chemical has a long half-life cumulative exposure over time can be assessed as well.

Hypotheses about the relationship between environmental risk factors and disease often are generated from ecologic studies and identification of clusters. Although useful if performed properly, both types of analyses have serious limitations and should be interpreted with caution. Ecologic studies are studies in which both disease and exposure are assessed on the group rather than on the individual level; regional rates of disease are compared to regional rates of the exposure. These studies are inexpensive to execute because they make use of available data and do not require extensive exposure assessment. However, the major problems are that proxies for individual exposure are often used, there is no way to know if the exposed people are really the ones who have the disease, and information on potential confounding factors is often unavailable.

A cluster is an excess of cases in space, in time, or in both space and time (51). The identification of a cluster is usually based on anecdotal evidence, and is dependent on how the geographic area or time frame is defined. Neutra and associates point out that the prior probability that a cluster is caused by environmental exposures is low because (*a*) carcinogens are usually present in the

environment in very low levels, and (*b*) many small areas will, by chance alone, have at least one type of cancer whose elevation is statistically significant (82). Despite these limitations, cluster analyses can identify previously unsuspected risk factors for further study.

GEOGRAPHIC VARIATION AND SUSPECTED CLUSTERS

Evidence of variation in geographic incidence and mortality rates of breast cancer within the United States and identification of suspected breast cancer clusters have stimulated interest in potential environmental risk factors for breast cancer. Breast cancer rates among older women have been reported to be higher in the Northeast than in the South and in urban areas compared to rural areas (11, 99). Blot et al reported that mortality rates of breast cancer (1950–1969) were 20% higher in large high-income counties (i.e. more urban) in the Northeast than in comparable counties in the South. Rates in smaller low-income counties in the North were as much as 49% higher than in the South (11). Using data from the National Center for Health Statistics from 1987, Sturgeon and associates observed elevated age-adjusted mortality rate ratios in all regions compared to the South for women aged 50 to 79. The relative risks were 1.30 in the Northeast; 1.18 in the Midwest; and 1.15 in the West (99). Breast cancer mortality in younger (premenopausal) women did not vary by region in either study (11, 99). In a population-based study in New York State, Nasca and associates found a significantly increasing linear relationship between standardized incidence rates of breast cancer and population density, a proxy for urbanization (78).

To determine the likelihood of an environmental explanation for these observations, nationwide studies have focused on evaluating the contribution of already established breast cancer risk factors to these observed patterns of risk. In the Blot et al study the relationship between mortality and region remained significant after adjustment for demographic, socioeconomic, ethnicity, and fertility variables defined crudely from county-level census data (11). Sturgeon et al used data from the 1987 National Health Interview Survey to describe the average breast cancer risk factor profile for each region of the continental United States. In an ecological analysis controlling for group-defined risk and prognostic factors, they were able to explain 50% of the excess mortality in the Northeast and Midwest and 10% in the West (99). We performed a prospective analysis of national breast cancer incidence rates utilizing individual-level information on breast cancer risk factors in a defined cohort. The study population was the Nurses' Health Study, a large cohort of 121,700 women residing in 11 states grouped according to region. We did not observe an excess in breast cancer

incidence in either the Northeast or the Midwest compared to the South. However, age-adjusted incidence rates among postmenopausal women in California (the only state from the West) were modestly elevated compared to the South (RR = 1.24, 95%CI = 1.05–1.47). After adjusting for breast cancer risk factors, this excess rate was attenuated by 25% (RR = 1.18, 95%CI = 1.00–1.40) (58). Consistent with these findings, the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute reported high breast cancer incidence in the San Francisco Bay Area compared to the other seven registries located throughout the country (RR = 1.14 and 1.10 for white and African American women, respectively) (87a). A recent study showed that regional differences in known breast cancer risk factors completely accounted for this modest elevation (87a). Based on the results from the Sturgeon and Laden studies, region-specific widespread environmental pollutants are unlikely to be responsible for reported differences in breast cancer incidence and mortality rates in the United States.

Garland et al hypothesized that the excess breast cancer mortality observed in urban areas and in the Northeast compared to the South could be due to differences in exposure to sunlight (37). Sunlight is necessary for synthesis of vitamin D in the skin, and in vitro studies have suggested that vitamin D inhibits growth of breast cancer cells in culture (33). Annual levels of sunlight were inversely correlated with age-adjusted mortality rates in urban areas ($r = -0.8$) and in rural areas ($r = -0.5$) (37). These researchers also observed similar results in a study in the USSR (40).

Breast cancer clusters provide the opportunity to study suspected ambient environmental exposures at the local level. At least three potential clusters have been discussed in peer-reviewed journals. In 1978, very small quantities of various polycyclic aromatic hydrocarbons (PAHs) were detected in wells in the city of St. Louis Park, a suburb of Minneapolis. Elevated breast cancer cases were initially observed in this city when compared to nearby areas (32). However, once the incidence ratios were adjusted for known risk factors for breast cancer by determining their prevalence from interviews of a sample of the cases and using relative risks from the literature, the number of observed cases was not different from expectation (27).

In response to concerns of Long Island residents about higher than average breast cancer incidence in Nassau County, the western part of the Island, the National Cancer Institute and the National Institute of Environmental Health Sciences have undertaken an extensive breast cancer case-control study. The study will examine the association of breast cancer risk with exposures to contaminated drinking water; indoor and ambient air pollution, including pesticide levels in household dust; electromagnetic fields; and hazardous and municipal wastes (52). In a previous case-control study performed by the New York State

Department of Health, an increased risk of breast cancer, adjusted for known breast cancer risk factors, was observed among postmenopausal women who had ever lived near a chemical facility in Nassau County in the past 20 years (OR = 1.61, 95%CI = 1.06–2.43) (59). There was evidence of a "dose-effect;" risk increased with number of chemical facilities and how long they lived there. An elevated, but nonsignificant risk was also observed for residence near areas of high traffic density. A cluster analysis of counties in the Northeast United States suggests that the elevated breast cancer mortality observed on Long Island might be part of a larger cluster encompassing the New York City-Philadelphia metropolitan area (56a).

Nine towns on Cape Cod, Massachusetts, had high breast cancer incidence in the period 1982–1990 compared to other communities in the state. No increase in breast cancer risk was found for women living near cranberry cultivation areas, which have been hypothesized to result in exposure to pesticides (4). A modest, but statistically nonsignificant elevation in risk was observed for women living near the gun and mortar positions at the Massachusetts Military Reservation (84), which might represent exposure to 2,4-dinitrotoluene, a probable human carcinogen. Research is ongoing (14).

Cancer rates associated with residence near known sources of pollution have also been evaluated elsewhere. Griffith et al compared age-adjusted breast cancer mortality rates in counties with trichlorethylene-contaminated groundwater from hazardous waste sites with rates in unexposed counties. They observed a statistically significant association for breast cancer (41). However, there was no evidence of an association between breast cancer incidence and residence near a municipal solid waste landfill in Montreal, Canada (38).

To date, no clear evidence in support of a causal association of general chemical exposures in the air or drinking water with increased breast cancer risk has emerged; much of the observed variation in rates appears to be due to known risk factors or chance. However, more thorough individual exposure assessments currently being performed, most notably the Long Island Study, should add substantial information in the near future.

ORGANOCHLORINES

Epidemiologic studies of breast cancer and environmental exposures to synthetic chemicals have focused on biologically persistent organochlorines. This class of compounds includes pesticides, e.g. 2,2-bis(p-chlorophenyl)-1,1,1-trichloromethane (DDT), chlordane, hexachlorocyclohexane (HCH, lindane), hexachlorobenzene (HCB), kepone, and mirex; industrial chemicals, e.g. polychlorinated biphenyls (PCBs); and dioxins (polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzodioxin (PCDDs)), produced as

combustion byproducts of PCBs or contaminants of pesticides. Another industrial chemical group, polybrominated biphenyls (PBBs), has also been studied. Many of these chemicals are weakly estrogenic (26) and are therefore hypothesized to increase breast cancer risk by mimicking 17β-estradiol. Furthermore, they are excreted in breast milk, suggesting that ductal and other cells in the breast are exposed directly. Other compounds, specifically the dioxins (50) and some PCB congeners (121), exhibit antiestrogenic activity; therefore, despite the established carcinogenicity of dioxin in animal tests (39), they might be protective for breast cancer.

The organochlorines are highly lipophilic and resistant to metabolism. Thus, many of these compounds bioaccumulate in the food chain and persist in the body and in the environment. The concentrations of these chemicals can be measured in breast milk, adipose tissue, and blood. Most of the epidemiologic literature on organochlorines focuses on DDT, DDE [1,1-dichloro-2,2,-bis(p-dichlorophenyl)ethylene, the main metabolite of DDT], and PCBs because they are among the most persistent in humans (63). Initial and ending dates of use of DDT and PCBs in the United States are presented in Table 1.

The general population is thought to be exposed to these compounds predominantly through ingestion of fish, dairy products, and meat. Almost everyone in the United States has had some measurable exposure; however, the average body burden of some of these chemicals (e.g. DDT) has been decreasing with time since the cessation of use in this country (57). The experimental and epidemiologic evidence of potential links to cancer has been reviewed in detail elsewhere by Adami et al (1), Ahlborg et al (3), and Wolff and associates (120), among others.

Ecological Studies

Several ecological studies focusing on exposure to organochlorines through diet have been performed. Westin & Richter observe a positive correlation of age-specific breast cancer mortality rates in Israel with trends in DDT and other pesticide contamination in milk (119). However, they evaluated estimates based on only two years of data. Using more extensive mortality and incidence data, Shames and associates did not observe an association (95).

Consumption of PCB-contaminated fatty fish from the Baltic Sea on the Swedish east coast and breast cancer has been assessed. In a cohort study comparing breast cancer rates among fishermen's wives from the east coast with rates among fishermen's wives from the noncontaminated west coast, the relative risk was 1.35 (95%CI = 0.98–1.86) (90). However, there was no control for other known breast cancer risk factors.

An accidental explosion in a chemical plant near Seveso, Italy, in 1976 provided the opportunity to evaluate exposure to high levels of dioxin in the

environment. Bertazzi et al studied both mortality (10) and cancer incidence (8) during the decade after the accident. Breast cancer incidence in the areas closest to the accident was slightly, but not significantly, lower than expected (8).

Occupational Studies

Studies of occupational exposure to organochlorines have not supported an association with elevated breast cancer risk. Fewer cases than expected were observed in studies of women occupationally exposed to phenoxy herbicides (68, 93), and PCBs (9, 15, 18). A twofold increase of breast cancer mortality was found in facilities with herbicide and dioxin exposures (70). However, only 7% of the participants worked in high-exposure areas. These studies are limited owing to the difficulties of exposure assessment and the small numbers of women employed in the occupations with greatest exposure.

Population-Based Case-Control Studies

To date, at least six small case-control studies, with between 9 and 44 breast cancer cases each, have evaluated organochlorine levels in adipose tissue. Although the results have been mixed, there is a suggestion that DDE (30, 34, 76, 116), PCBs (34, 116), HCB (30), and β-HCH (77) levels in women diagnosed with breast cancer are elevated compared with levels in controls. Other studies did not observe a significant difference for DDT (24), DDE, or PCBs (110). Furthermore, a recent large European case-control study (265 cases) reported a significantly inverse trend between levels of adipose DDE and risk of breast cancer after controlling for known breast cancer risk factors; the authors did not evaluate PCBs (112a). No difference was found between cases and controls for most isomers of the dioxins, PCDDs and PCDFs. However, in one study, contrary to expectation, the levels of octachlorinated dibenzo-p-dioxin (OCDD) were slightly elevated in the cases (45).

There is some evidence of an association of DDE levels with estrogen-receptor status in breast tumors. Dewailly et al observed a statistically significant elevation in DDE levels among estrogen receptor-positive cases ($n = 18$) only (30), and the estrogen receptor concentrations were significantly correlated with levels of DDE (29). Total PCBs were nonsignificantly elevated in estrogen receptor-positive cases (30).

Three prospective studies have used stored blood samples collected prior to diagnosis to evaluate the relationship between DDE and total PCBs with breast cancer (56, 122). Results have been inconclusive. In a cohort in New York City of 14,290 women (80% of whom were Caucasian), levels in sera from 58 women diagnosed within 1–6 months of blood collection in 1985 to 1991 were compared with levels among 171 controls. Mean levels of DDE were 35% higher in cases than controls ($p = 0.03$) and mean levels of total

PCBs were 15% higher in cases ($p = 0.06$). In conditional analyses, adjusting for family history of breast cancer, lifetime lactation, and age at first full-term pregnancy, the odds ratio for the tenth decile of DDE compared to the first was 4.08 (95%CI = 1.49–11.20), and the positive trend was statistically significant. The equivalent odds ratio for PCBs was not statistically significant (OR = 1.70, 95%CI = 0.79–3.68).

In another prospective study, Krieger et al examined sera selected from a cohort of 57,040 San Francisco Bay Area women who had provided blood in the late 1960s, when DDT and PCBs were still in production (56). From a large number of incident cases diagnosed more than six months after blood draw and prior to 1991, 50 white, 50 African American, and 50 Asian cases were selected and compared with 150 age- and ethnicity-matched control women. Conditional logistic analyses comparing the third tertile of DDE to the first and the third tertile of PCBs to the first, controlling for breast cancer risk factors, did not indicate an increased risk associated with either compound when all ethnic groups were combined (DDE: OR = 1.33, 95%CI = 0.68–2.62; PCBs: OR = 0.94, 95%CI = 0.48–1.84). However, ethnicity-specific analyses indicated nonsignificant elevated risk associated with DDE for African Americans and whites (African Americans: OR = 3.85, 95%CI = 0.93–16.05; whites: OR = 2.38, 95%CI = 0.54–10.64).

Hunter et al measured plasma levels of DDE and PCBs prospectively among 236 cases and their matched controls in the Nurses' Health Study (described previously). Bloods were collected in 1989 to 1990, at least 1 month before disease diagnosis. There was no evidence of a positive association of breast cancer with either DDE or PCBs. The multivariate relative risks for women in the highest quintile compared to women in the lowest were 0.72 (95%CI = 0.37– 1.40) for DDE, 0.66 (95%CI = 0.32–1.37) for PCBs. For women in the highest quintiles of both DDE and PCBs the relative risk was 0.43 (95%CI = 0.13–1.44) for joint exposure (50a).

An additional prospective study focused on environmental exposures to polybrominated biphenyls (PBBs). This case-control study is nested in a Michigan-based cohort of 1925 women enrolled in a PBB registry because of exposure to PBB-contaminated meat and dairy products. Serum PBB levels in 20 breast cancer cases were elevated compared to 290 matched controls (47). The odds ratio for women with serum PBB levels greater than or equal to 2 ppb compared with women with lower serum PBB levels was 3.3 (95% CI = 0.9–11.4); however, there was no evidence of a dose-response relationship.

Research in this area is ongoing and a number of analyses should be available in the next 1–2 years. In a preliminary report from Buffalo, New York, Moysich et al evaluated lipid-adjusted serum levels of DDE, HCB, Mirex, and total PCBs among 154 incident breast cancer cases and 192 community controls. There was no evidence of a positive association between any of these compounds

and breast cancer risk with the possible exception of lower chlorinated PCBs (OR = 1.66, 95%CI = 0.99–2.88) (75). However, among women who had never breast fed there was a suggestion of increased risk of breast cancer, with higher serum levels of total PCBs (OR = 2.92, 95%CI = 0.95–11.35). The odds ratio was even higher when the PCBs considered were restricted to higher chlorinated congeners (OR = 4.15, 95%CI = 0.99–10.55) (74). Lopez-Carrillo and coworkers analyzed serum DDT levels in a case-control study in Mexico, where the pesticide is still in use (66). The results were not consistent with an increased risk of breast cancer due to DDT exposure; the odds ratio comparing the first tertile with the third was 0.97 (95%CI = 0.55–1.70).

In summary, most of the recent large studies have not found evidence of increased breast cancer risk associated with blood levels of DDE or total PCBs. The possibility that a positive association might be limited to women with particular reproductive characteristics [e.g. women who have never breast fed, as observed by Moysich (74)] should be examined carefully in the large ongoing studies. Nonetheless, it appears that these environmental exposures are unlikely to be responsible for rising breast cancer rates.

IONIZING RADIATION

The carcinogenic effects of ionizing radiation in general and the sensitivity of breast tissue to radiation are well established. Radiation is ubiquitous in the environment from natural sources, which include cosmic rays, terrestrial radiations influenced by the distribution of radioactive elements in the soil, and internally deposited radionuclides, such as radon. The average annual dose to the US population from these natural background sources is approximately 3 mSv (millisievert) per year (80). Health effects associated with low exposures are difficult to evaluate, because the levels are hard to measure and it is hard to find an unexposed group. However, single large-dose exposures to ionizing radiation from the atomic bomb blasts in Hiroshima and Nagasaki, and repeated exposures from therapeutic regimes, such as treatment for tuberculosis, post-partum mastitis, and cervical cancer, are an established cause of breast cancer. A linear dose response is consistently observed, with relative risks as high as 6.4 reported for exposure to at least 4 Gy (gray) (see References 12, 53 for comprehensive reviews).

Estimates of the effects of low doses have been extrapolated from the results of the atomic bomb and medical radiation studies (12, 79). Based on this literature, Boice and associates estimated that the relative risk of breast cancer mortality associated with 1 Gy of radiation ranges from 1.1 to 2.7 (depending mainly on age distributions and follow-up times), and the excess risk ranges from 3.5 to 18 $\times$ 10^4 person years/Gy (12). There is convincing evidence that age at exposure influences the relative risk. The excess risk decreases with

increasing age at exposure; the highest relative risks are observed for women exposed between the ages of 10 and 20, and there is little risk for those greater than 40 (102).

There is little reliable evidence of an increased risk of breast cancer due to occupational exposures to radiation. A potential cluster of breast cancer cases was identified at a nuclear facility in Washington State, but a case-control study did not elucidate any significant association with cumulative radiation dose (113). Exposure to both internal and external radiation has been evaluated in radium dial workers. Breast cancer incidence was elevated in exposed women employed before 1930 (2); however, the incidence did not decrease coincident with a decrease in radium intake levels (97). An additional study observed a statistically significant unadjusted excess risk of breast cancer for women exposed in their 20s to at least 0.2 Gy γ-rays externally (SIR = 1.44) (6). Airline attendants are also exposed to gamma radiation. In a Finnish study, an elevated risk of breast cancer (SIR = 1.87; 95%CI = 1.15–2.23) was observed; however, the authors themselves argue that residual confounding by socioeconomic status and parity could explain these results (86). In a case-control study of women employed as radiologic technologists, breast cancer risk was not associated with personal exposure to radiation as defined by job history and length of employment (13, 31).

There has been no evidence of excess breast cancer mortality among the general population from low-dose environmental radiation exposures such as fallout from nuclear weapons testing and nuclear installations (79). Ecological studies comparing breast cancer incidence in the five years before and the six years after the Three Mile Island accident (7) and in Iowa counties with estimated high and low home radon exposure (81) also did not report an excess risk.

Radiation is a known breast carcinogen, and high doses associated with medical exposure at a young age can lead to large relative risks. However, occupational studies have been inconclusive. Furthermore, there is no evidence of increased risk associated with exposures experienced by the general public, even in areas known to have elevated radiation levels due to industrial accidents or nuclear activities.

ELECTROMAGNETIC FIELDS

The electrification of America began in 1880 with nighttime street lighting systems, and by the beginning of the 1930s, many electrical appliances had been introduced into the home. Use of electric power grew steadily throughout the century, approximately 7% to 13% per year, until the 1970s (108; see Table 1 for more historical information).

Alternating currents from electric power facilities and household appliances produce electric and magnetic fields (i.e. electromagnetic fields, EMF) in the extremely low-frequency range (60 Hz in the United States, 50 Hz in European countries). Exposure to environmental lighting in the visible range of the spectrum (20) and low-level EMF (98) have been hypothesized to increase the risk of breast cancer due to a decrease in the secretion of the hormone melatonin and a subsequent increase in circulating estrogens. In seasonal breeding mammals, melatonin, which has a distinct circadian rhythm, relays environmental cues to the reproductive system by regulating the release of prolactin, estrogen, and testosterone (100, 123). In addition, melatonin has been identified as a hydroxyl radical scavenger; thus, its suppression could result in increased carcinogenesis due to increased oxidative damage (87). Although there is little experimental human evidence, in vitro and in vivo studies in animals have demonstrated a link among EMF, melatonin, and breast cancer (5, 62; reviewed in 61, 67).

Occupational Studies

To date, most of the epidemiologic studies of EMF exposure and breast cancer have evaluated risk in populations employed in electrical occupations (e.g. electricians, telephone linemen, communication workers, railroad workers, and power plant operators). The results have been inconsistent. Evidence of an elevated risk of male breast cancer associated with presumed occupational EMF exposure based on job title has been observed in four cohort studies (28, 35, 71, 103), with measures of association ranging from 1.2 to 6.5. Loomis et al (64) observed similar results for younger (based on 1 case) but not for older men. Because male breast cancer is a relatively rare disease, these results are based on small numbers of cases and are therefore very unstable. In a large cohort study of cancer incidence in Denmark, occupational codes from the census were grouped according to probable exposure to type and level of EMF exposure. The risk of breast cancer in men associated with exposure to continuous magnetic fields greater than 0.3 mT (micro-tesla) was elevated slightly, although confidence intervals were wide (SIR = 1.4; 95%CI = 0.2–4.9) (43). Other cohort studies of general male cancer mortality (42, 83, 111) and incidence (112) have not reported any male breast cancer cases. Rosenbaum and coworkers in a New York State–based case-control study did not observe an elevated risk of male breast cancer incidence associated with occupational EMF exposure (89). A case-control study of electric utility workers in three facilities in Canada and France observed too few cases to perform a formal analysis (101). No evidence of an increased risk of breast cancer was observed in the cohort studies, which also included female employees (43, 111, 112).

Four case-control studies were designed specifically to study occupational exposure to EMF and breast cancer in women (Table 2). Loomis and coworkers

Table 2 Case-control studies of occupational exposure to electromagnetic fields (EMF) and female breast cancer

Reference	Population in United States	Comparison group	Risk factors controlled for	Exposure assessment	Definition of exposure	Study size	Result (95% CI)
Loomis et al 1994 (65)	24 states, NCHS[a]	Other deaths	Age, race, SES[b], marital status	Death certificates	Electrical occupations	28,434 cases 113,011 controls	OR = 1.4 (1.0–1.8)
Cantor et al 1995 (17)	24 states, NCHS	Other deaths	Age, race, SES	Death certificates	High-level ELF[c] EMF	Whites: 29,397 cases 102,955 controls	OR = 1.0 (0.8–1.2)
						African Americans: 4112 cases 14,839 controls	OR = 1.2 (0.7–2.1)
					High probable ELF EMF	Whites: (see above)	OR = 1.1 (1.0–1.2)
						African Americans: (see above)	OR = 1.3 (1.1–1.6)
Cantor et al 1995 (18)	24 states, NCHS	Other deaths	Age, race, SES	Death certificates	High-level radiofrequency EMF	Whites: (see above)	OR = 1.1 (1.1–1.2)
						African Americans: (see above)	OR = 1.3 (1.1–1.5)
Coogan et al 1996 (23)	Residents ME, WI, MA, NH	Population controls	Age, state, brca[d] risk factors	Work history, interview	Jobs with high EMF exposure	6888 cases 9529 controls	OR = 1.4 (1.0–2.1)

[a]NCHS = National Center for Health Statistics; [b]SES = socioeconomic status; [c]ELF = extremely low frequency; [d]brca = breast cancer.

(65) observed a statistically significant 40% excess risk of breast cancer mortality among women in electrical occupations. In an independent study using the same database with an additional year of follow-up and more detailed exposure assessment, Cantor et al evaluated level and probability of exposure separately for extremely low frequency fields (ELF) (17) and EMF in the radiofrequency range (18). These researchers did not observe an association of breast cancer mortality with higher levels of exposure to ELF fields (17). They did find a small, statistically significant risk elevation for the highest level of exposure to radiofrequency EMF among white and African American women, but no evidence of a dose response (18). Coogan and associates obtained information on usual occupation, job duties, and breast cancer risk factors from telephone interviews (23). Like Loomis, they reported a statistically significant 40% excess risk of breast cancer associated with exposure.

In all of the above studies misclassification of exposure is a major concern. The exposure classifications are based on the subjects' "usual" occupation, often obtained from death certificates. Many assessments relied on groupings of job titles with heterogeneous exposures. Duration, timing, and an individual's personal work tasks could not be accounted for in most of the studies, and with the exception of small sub-studies performed in conjunction with four of the analyses (35, 43, 71, 101), no actual EMF measurements were obtained. However, any misclassification that does occur will most likely be nondifferential, resulting in an attenuation of the relative risks. With the exception of the Coogan study (23), adjustment for known breast cancer risk factors was limited.

Other Epidemiological Studies

The general population is exposed to EMF primarily from power lines, transformer substations, and electrical appliance use. In a 1987 study of mortality from all cancer subtypes and residential wiring configurations, Wertheimer & Leeper observed a statistically significant elevation in female breast cancer incidence associated with magnitude of exposure at the current residence (118). Cohort studies in Britain (72) and the Netherlands (94) did not observe an association between female breast cancer deaths and residence in the vicinity of electricity transmission facilities. A case-control study in Taiwan also did not report any elevation in female breast cancer incidence with exposure to EMFs determined either from distance of the residence to transmission lines or from estimated magnetic field levels (60). Again, there are potential problems with nondifferential exposure misclassification in these studies. Individuals spend varying amounts of time at home, actual EMF exposure decreases quickly with distance from the source, and the residence evaluated may not be relevant in terms of the timing of disease initiation or onset.

Use of electric blankets produced before 1990 throughout the night was estimated to double an individual's average exposure to EMFs (36, 85). Furthermore, exposure typically takes place at night when the natural melatonin peak occurs and the blanket is placed close to the body. Vena and coworkers performed a case-control study focusing on exposure to electric blankets (114, 115). They found that the use of electric blankets continuously throughout the night was associated with a nonstatistically significant increase in postmenopausal breast cancer (OR = 1.46, 95%CI = 0.96–2.20) (115) and for premenopausal breast cancer (OR = 1.43, 95%CI = 0.94–2.17) (114) compared to never users. Additional studies of electric blanket exposure and other residential exposures to EMF and breast cancer risk are ongoing.

PASSIVE SMOKING

Few studies have evaluated the relationship between passive smoking and breast cancer. Like mainstream smoke, sidestream smoke contains ammonia, volatile amines, volatile nitrosamines, nicotine decomposition products, and aromatic amines. Data from animal models have suggested that sidestream smoke contains more carcinogenic activity per milligram than does mainstream smoke (109). Therefore, passive smoke inhalation can represent a measurable source of exposure to these carcinogens.

There is a suggestion that women married to smokers experience a modest increased risk of breast cancer. A cohort study of cancer mortality among Japanese women reported a possible risk elevation (crude RR = 1.3, 95%CI = 0.8–2.0) (49, 117). In a case-control study, Sandler and coworkers observed an odds ratio of 1.8 (95%CI = 1.0–3.7), adjusted for age and education (91). They also observed a significant linear trend with number of household exposure sources (92). Wells combined the data from the Hirayama and Sandler studies and estimated a 40% elevation of breast cancer risk associated with living with a smoker (117). Results from two recent case-control studies with extensive evaluation of lifetime exposures to passive smoke and of potential confounding by breast cancer risk factors, including alcohol consumption, are consistent with an increased risk. Smith et al observed an approximately threefold increase of breast cancer among young women (<36 years) passively exposed to greater than 400 cigarette-years (OR = 2.7, 95%CI = 1.1–6.6). However, there was no evidence of a dose-effect (96). Morabia and associates observed a similar elevated OR for ever exposed versus never exposed women aged 30–75 at diagnosis (OR = 3.2, 95%CI = 1.7–5.9) (73).

Despite these positive associations, and despite the differences in chemical composition of environmental and direct smoke, the great majority of studies of direct smoking and breast cancer have not observed any association. It is difficult to reconcile the absence of an effect of heavy smoking for decades

with an effect of exposure to much lower amounts of environmental smoke. However, this association should be studied further in some of the large ongoing breast cancer studies.

OVERALL DISCUSSION AND CONCLUSIONS

In general, the state of the evidence does not support a substantial relationship between the environment and breast cancer risk. Breast cancer mortality and incidence varies modestly throughout the country. However, lifestyle patterns influencing reproductive breast cancer risk factors explain a large proportion of the differences, and are therefore more likely to be responsible for this pattern than differences in widespread regional level environmental pollution. Results from studies of exposure to organochlorines have been inconclusive; the most recent evidence in prospective analyses does not support an association with breast cancer risk. Ionizing radiation is a known risk factor for breast cancer, but the levels to which the general population is exposed are too low to cause an effect. Occupational studies of EMF exposure have been inconclusive; however, residential studies imply that there is no risk associated with overhead power lines. Electric blanket users might experience some increased risk over nonusers, but these results require replication. Women exposed to passive smoke could experience an increased risk of breast cancer, but there is no evidence of a dose-effect, and results from studies of direct smoking are not as strong.

Ambient environmental exposures are difficult to measure, and in general levels are low. It is possible to miss a real effect due to nondifferential misclassification of exposure. Furthermore, the exposure definitions commonly used might be inaccurate. For example, most studies have grouped the PCB congeners together and evaluated exposure to "total PCBs." Some of these congeners show evidence of antiestrogenic activity. Therefore, including them with estrogenic congeners could mask a causal relationship. Also, these studies may not be evaluating exposure at the appropriate time in the development of breast cancer; exposures early in life or in utero might be more relevant.

The four pollutants discussed here have been considered as potential breast cancer risk factors based on biological hypotheses. It is possible that there are other environmental exposures that have not been identified that warrant evaluation. Further study utilizing better exposure assessment and focusing on timing of exposures is needed. However, based on current evidence, with the exception of ionizing radiation, no environmental exposures can be confidently labeled as a cause of breast cancer.

ACKNOWLEDGMENTS

Our work was supported in part by National Cancer Institute Grants CA/ES62984 and CA40356. Francine Laden was also supported by an

Institutional National Research Service Award in Cancer Epidemiology, 5T32CA09001. David Hunter was also supported by American Cancer Society Faculty Research Award FRA-455. We thank Sarah Corey and Tracey Corrigan for assistance in manuscript preparation.

Literature Cited

1. Adami H-O, Lipworth L, Titus-Ernstoff L, Hsieh C-C, Hanberg A, et al. 1995. Organochlorine compounds and estrogen-related cancers in women. *Cancer Causes Control* 6:551–66
2. Adams EE, Brues AM. 1980. Breast cancer in female radium dial workers first employed before 1930. *J. Occup. Med.* 22:583–87
3. Ahlborg UG, Lipworth L, Titus-Ernstoff L, Hsieh C-C, Hanberg A, et al. 1995. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. *Crit. Rev. Toxicol.* 25:463–531
4. Aschengrau A, Ozonoff D, Coogan P, Vezina R, Heeren T, Zhang Y. 1996. Cancer risk and residential proximity to cranberry cultivation in Massachusetts. *Am. J. Public Health* 86:1289–96
5. Baum A, Mevissen M, Kamino K, Mohr U, Loscher W. 1995. A histopathological study on alterations in DMBA-induced mammary carcinogenesis in rats with 50 Hz, 100 μT magnetic field exposure. *Carcinogenesis* 16:119–25
6. Baverstock KF, Papworth D, Vennart J. 1981. Risk of radiation at low dose rates. *Lancet* 1:430–33
7. Berkheiser SW. 1987. Breast cancer incidence and the TMI accident. *Pa. Med.* 90:40, 2
8. Bertazzi PA, Pesatori AC, Consonni D, Tironi A, Landi MT, Zocchetti C. 1993. Cancer incidence in a population accidentally exposed to 2,3,7,8-tetrachlorodibenzo-para-dioxin. *Epidemiology* 4:398–406
9. Bertazzi PA, Riboldi L, Pesatori A, Radice L, Zocchetti C. 1987. Cancer mortality of capacitor manufacturing workers. *Am. J. Ind. Med.* 11:165–76
10. Bertazzi PA, Zocchetti C, Pesatori AC, Guercilena S, Sanarico M, Radice L. 1989. Ten-year mortality study of the population involved in the Seveso Incident in 1976. *Am. J. Epidemiol.* 129:1187–200
11. Blot WJ, Fraumeni JF, Stone BJ. 1977. Geographic patterns of breast cancer in the United States. *J. Natl. Cancer Inst.* 59:1407–11
12. Boice JD Jr, Land CE, Preston DL. 1996. Ionizing radiation. In *Cancer Epidemiology and Prevention*, ed. D Schottenfeld, JF Fraumeni Jr, pp. 319–72. New York: Oxford Univ. Press. 2nd ed.
13. Boice JD, Mandel JS, Doody MM. 1995. Breast cancer among radiologic technologists. *JAMA* 274:394–401
14. Brody JG, Rudel R, Maxwell NI, Swedis SR. 1996. Mapping out a search for environmental causes of breast cancer. *Public Health Rep.* 111:494–507
15. Brown DP. 1987. Mortality of workers exposed to polychlorinated biphenyls—an update. *Arch. Environ. Health* 42: 333–39
16. Buell P. 1973. Changing incidence of breast cancer in Japanese-American women. *J. Natl. Cancer Inst.* 51:1479–83
17. Cantor KP, Dosemeci M, Brinton LA, Stewart PA. 1995. Re: Breast cancer mortality among female electrical workers in the United States (correspondence). *J. Natl. Cancer Inst.* 87:227–28
18. Cantor KP, Stewart PA, Brinton LA, Dosemeci M. 1995. Occupational exposures and female breast cancer mortality in the United States. *J. Occup. Environ. Med.* 37:336–48
19. Chudacoff HP. 1981. *The Evolution of American Urban Society*. Englewood Cliffs, NJ: Prentice-Hall. 312 pp. 2nd ed.
20. Cohen M, Lippman M, Chabner B. 1978. Role of pineal gland in aetiology and treatment of breast cancer. *Lancet* 2:814–16
21. Colditz GA, Frazier AL. 1995. Models of breast cancer show that risk is

set by events of early life: Prevention efforts must shift focus. *Cancer Epidemiol. Biomarkers Prev.* 4:567–71
22. Coleman MP, Esteve J, Damiecki P, Arslan A, Renard H. 1993. *Trends in Cancer Incidence and Mortality. Rep. IARC Sci. Publ. No. 121*. Lyon, France: Int. Agency Res. Cancer
23. Coogan PF, Clapp RM, Newcomb PA, Wenzl TB, Bogdan G, et al. 1996. Occupational exposure to 60-hertz magnetic fields and risk of breast cancer in women. *Epidemiology* 7:459–64
24. Davies JE, Barquet A, Morgade C, Raffonelli A. 1976. Epidemiologic studies of DDT and dieldrin residues and their relationship to human carcinogenesis. Recent advances in assessment of health effects of environmental pollution, WHO, CEC, US EPA. *Int. Symp. Proc., Paris, June 24–28, 1974*. 11:695–702
25. Davis DL, Bradlow HL. 1995. Can environmental estrogens cause breast cancer? *Sci. Am.* 273:166–72
26. Davis DL, Bradlow HL, Wolff M, Woodruff T, Hoel DG, Anton-Culver H. 1993. Medical hypothesis: xenoestrogens as preventable causes of breast cancer. *Environ. Health Perspect.* 101:372–77
27. Dean AG, Imrey HH, Dusich K, Hall WN. 1988. Adjusting morbidity ratios in two communities using risk factor prevalence in cases. *Am. J. Epidemiol.* 127:654–62
28. Demers PA, Thomas DB, Rosenblatt KA, Jimenez LM, McTiernan A, et al. 1991. Occupational exposure to electromagnetic fields and breast cancer in men. *Am. J. Epidemiol.* 134:340–47
29. Dewailly E, Ayotte P, Dodin S. 1997. Could the rising levels of estrogen receptor in breast cancer be due to estrogenic pollutants? *J. Natl. Cancer Inst.* 89:888–89
30. Dewailly E, Dodin S, Verreault R, Ayotte P, Sauve L, Morin J. 1994. High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J. Natl. Cancer Inst.* 86:232–34
31. Doody MM, Mandel JS, Boice JD. 1995. Employment practices and breast cancer among radiologic technologists. *J. Occup. Environ. Med.* 37:321–27
32. Dusich K, Sigurdson E, Hall WN, Dean AG. 1980. Cancer rates in a community exposed to low levels of creosote components in municipal water. *Minn. Med.* 63:803–6
33. Eisman JA, McIntyre I, Martin TJ, Frampton RJ, King RJ. 1980. Normal and malignant breast tissue is a target organ for 1,25-$(OH)_2$ vitamin D_3. *Clin. Endocrinol.* 13:267–72
34. Falck F, Ricci A, Wolff MS, Godbold J, Deckers P. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health* 47:143–46
35. Floderus B, Tornqvist S, Stenlund C. 1994. Incidence of selected cancers in Swedish railway workers, 1961–79. *Cancer Causes Control* 5:189–94
36. Florig HK, Hoburg JF. 1990. Power-frequency magnetic fields from electric blankets. *Health Phys.* 58:493–502
37. Garland FC, Garland CF, Gorham ED, Young JF. 1990. Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev. Med.* 19:614–22
38. Goldberg MS, Al-Homsi N, Goulet L, Riberdy H. 1995. Incidence of cancer among persons living near a municipal solid waste landfill site in Montreal, Quebec. *Arch. Environ. Health* 50:416–24
39. Goldstein JA, Safe S. 1989. Mechanism of action and structure-activity relationship for the chlorinated dibenzo-p-dioxins and related compounds. In *Halogenated Biphenyls, Terphenyls, Naphthalenes, Dibenzodioxins and Related Products*, ed. RD Kimbrough, AA Jensen, pp. 239–85. Amsterdam: Elsevier. 518 pp. 2nd ed.
40. Gorham ED, Garland FC, Garland CF. 1990. Sunlight and breast cancer incidence in the USSR. *Int. J. Epidemiol.* 19:820–24
41. Griffith J, Duncan RC, Riggan WB, Pellom AC. 1989. Cancer mortality in US counties with hazardous waste sites and ground water pollution. *Arch. Environ. Health* 44:69–74
42. Guberan E, Usel M, Raymond L, Tissot R, Sweetnam P. 1989. Disability, mortality, and incidence of cancer among Geneva painters and electricians: a historical prospective study. *Br. J. Ind. Med.* 46:16–23
43. Guenel P, Raskmark P, Andersen JB, Lynge E. 1993. Incidence of cancer in persons with occupational exposure to electromagnetic fields in Denmark. *Br. J. Ind. Med.* 50:758–64
44. Hahn RA, Moolgavkar S. 1989. Nulliparity, decade of first birth, and breast cancer in Connecticut cohorts

1855–1945: an ecological study. *Am. J. Public Health* 79:1503–7

45. Hardell L, Lindstrom G, Liljegren G, Dahl P, Magnuson A. 1996. Increased concentrations of octachlorodibenzo-p-dioxin in cases with breast cancer—results from a case-control study. *Eur. J. Cancer Prev.* 5:351–57
46. Harris JR, Lippman ME, Veronesi U, Willett W. 1992. Breast cancer. *N. Engl. J. Med.* 327:319–28
47. Henderson AK, Rosen D, Miller GL, Figgs LM, Zahm SH, et al. 1995. Breast cancer among women exposed to polybrominated biphenyls. *Epidemiology* 6:544–46
48. Heston JF, Kelly JAB, Meigs JW, Flannery JT. 1986. *Forty-five Years of Cancer Incidence in Connecticut: 1935–79. Rep. 70*, Natl. Cancer Inst., Bethesda, MD
49. Hirayama T. 1984. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. *Prev. Med.* 13:680–90
50. Holcomb M, Safe S. 1994. Inhibition of 7,12-dimethylbenzanthracene-induced rat mammary tumor growth by 2,3,-7,8-tetrachlorodibenzo-p-dioxin. *Cancer Lett.* 82:43–47

50a. Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JE, et al. 1997. Plasma organochlorine levels and risk of breast cancer in a prospective study. *N. Engl. J. Med.* 337:1253–58

51. Jacquez GM, Waller LA, Grimson R, Wartenberg D. 1996. The analysis of disease clusters, part I: state of the art. *Infec. Control Hosp. Epidemiol.* 17:319–27
52. Jenks S. 1994. Researchers to comb Long Island for potential cancer factors. *J. Natl. Cancer Inst.* 86:88–89
53. John EM, Kelsey JL. 1993. Radiation and other environmental exposures and breast cancer. *Epidemiol. Rev.* 15:157–62
54. Kelsey JL, Horn-Ross PL. 1993. Breast cancer: magnitude of the problem and descriptive epidemiology. *Epidemiol. Rev.* 15:7–16
55. Kosary CL, Ries LAG, Miller BA, Hankey BF, Harras A, Edwards BK, eds. 1995. *SEER Cancer Statistics Review, 1973–1992, Tables and Graphs, Natl. Cancer Inst. NIH Publ. No. 96–2789*, Bethesda, MD
56. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. 1994. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J. Natl. Cancer Inst.* 86:589–99

56a. Kulldorff M, Feuer EJ, Miller BA, Freedman LS. 1997. Breast cancer clusters in the Northeast United States: a geographic analysis. *Am. J. Epidemiol.* 146:161–70

57. Kutz FW, Wood PH, Bottimore DP. 1991. Organochlorine pesticides and polychlorinated biphenyls in human adipose tissue. *Rev. Environ. Contam. Toxicol.* 120:1–82
58. Laden F, Spiegelman D, Neas LM, Colditz GA, Hankinson SE, et al. 1997. Geographic variation of breast cancer incidence rates in a cohort of US women. *J. Natl. Cancer Inst.* In press
59. Lewis-Michl EL, Melius JM, Kallenbach LR, Ju CL, Talbot TO, et al. 1996. Breast cancer risk and residence near industry or traffic in Nassau and Suffolk Counties, Long Island, New York. *Arch. Environ. Health* 51:255–65
60. Li C-Y, Theriault G, Lin RS. 1997. Residential exposure to 60-Hertz magnetic fields and adult cancers in Taiwan. *Epidemiology* 8:25–30
61. Liburdy RP, Loscher W. 1997. Laboratory studies on extremely low frequency (50/60-Hz) magnetic fields and carcinogenesis. In *The Melatonin Hypothesis, Breast Cancer and Use of Electric Power*, ed. RG Stevens, BW Wilson, LE Anderson, pp. 585–668. Columbus: Batelle Press. 760 pp.
62. Liburdy RP, Sloma TR, Sokolic R, Yaswen P. 1993. ELF magnetic fields, breast cancer, and melatonin: 60 Hz fields block melatonin's oncostatic action on ER+ breast cancer cell proliferation. *J. Pineal Res.* 14:84–97
63. Longnecker MP, Rogan WJ, Lucier G. 1997. The human health effects of DDT (dichlorodiphenyl-trichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. *Annu. Rev. Public Health* 18: 211–44
64. Loomis DP. 1992. Cancer of breast among men in electrical occupations. *Lancet* 339:1482–83
65. Loomis DP, Savitz DA, Ananth CV. 1994. Breast cancer mortality among female electrical workers in the United States. *J. Natl. Cancer Inst.* 86:921–25
66. Lopez-Carrillo L, Blair A, Lopez-Cervantes M, Cebrian M, Rueda C, et al. 1997. DDT serum levels and breast cancer risk: a case-control study from Mexico. *Cancer Res.* 57(17):3728–32
67. Loscher W, Mevissen M. 1994. Minire-

view: animal studies on the role of 50/60–Hertz magnetic fields in carcinogenesis. *Life Sci.* 54:1531–43
68. Lynge E. 1985. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. *Br. J. Cancer* 52:259–70
69. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. 1995. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J. Natl. Cancer Inst.* 87:1681–85
70. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 338:959–64
71. Matanoski GM, Breysse PN, Elliott EA. 1991. Electromagnetic field exposure and male breast cancer. *Lancet* 337:737
72. McDowall ME. 1986. Mortality of persons resident in the vicinity of electricity transmission facilities. *Br. J. Cancer* 53:271–79
73. Morabia A, Bernstein M, Heritier S, Khatchatrian N. 1996. Relation of breast cancer with passive and active exposure to tobacco smoke. *Am. J. Epidemiol.* 143:918–28
74. Moysich KB, Ambrosone CB, Vena JE, Kostyniak P, Shields PG, et al. 1997. Serum polychlorinated biphenyls (PCBs) and postmenopausal breast cancer risk. *Proc. Am. Assoc. Cancer Res.* 38:627 (Abstr.)
75. Moysich KB, Ambrosone CB, Vena JE, Shields PG, Marshall JR, et al. 1997. Serum organochlorine levels and postmenopausal breast cancer risk. *Am. J. Epidemiol.* 145:S20 (Abstr.)
76. Mussalo-Rauhamaa H. 1993. Selenium and DDE in breast fat of breast cancer patients: their relationship to hormone receptors in breast tissue (letter). *J. Natl. Cancer Inst.* 85:1964–65
77. Mussalo-Rauhamaa H, Hasanen E, Pyysalo H, Antervo K, Kauppila R, Pantzar P. 1990. Occurrence of beta-hexachlorocyclohexane in breast cancer patients. *Cancer* 66:2124–28
78. Nasca PC, Mahoney MC, Wolfgang PE. 1992. Population density and cancer incidence differentials in New York State, 1978–82. *Cancer Causes Control* 3:7–15
79. National Academy Press. 1990. *Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V)*. Washington, DC: Natl. Acad. Press. 421 pp.
80. National Council on Radiation Protection and Measurements. 1987. *Ionizing radiation exposures of the population of the United States. Rep. 93, Natl. Counc. Radiat. Prot. Meas.*, Washington, DC
81. Neuberger JS, Field RW. 1996. Radon and breast cancer [letter]. *Risk Anal.* 16:729–30
82. Neutra R, Swan S, Mack T. 1992. Clusters galore: insights about environmental clusters from probability theory. *Sci. Total Environ.* 127:187–200
83. Olin R, Vagero D, Ahlbom A. 1985. Mortality experience of electrical engineers. *Br. J. Ind. Med.* 42:211–12
84. Ozonoff D, Ashengrau A, Coogan P. 1994. Cancer in the vicinity of a department of defense superfund site in Massachusetts. *Toxicol. Ind. Health* 10:119–41
85. Preston-Martin S, Peters JM, Yu MC, Garabrant DH, Bowman JD. 1988. Myelogenous leukemia and electric blanket use. *Bioelectromagnetics* 9:207–13
86. Pukkala E, Auvinen A, Wahlberg G. 1995. Incidence of cancer among Finnish airline cabin attendants, 1967–92. *Br. Med. J.* 311:649–52
87. Reiter RJ. 1994. Melatonin suppression by static and extremely low frequency electromagnetic fields: relationship to the reported increased incidence of cancer. *Rev. Environ. Health* 10:171–86
87a. Robbins AS, Brescianini S, Kelsey JL. 1997. Regional differences in known risk factors and the higher incidence of breast cancer in San Francisco. *J. Natl. Cancer Inst.* 89:960–65
88. Roberts S. 1993. *Who We Are, A Portrait of America*. New York: Time Books/Random House. 306 pp.
89. Rosenbaum PF, Vena JE, Zielezny MA, Michalek AM. 1994. Occupational exposures associated with male breast cancer. *Am. J. Epidemiol.* 139:30–36
90. Rylander L, Hagmar L. 1995. Mortality and cancer incidence among women with a high consumption of fatty fish contaminated with persistent organochloride compounds. *Scand. J. Work Environ. Health* 21:419–26
91. Sandler DP, Everson RB, Wilcox AJ. 1985. Passive smoking in adulthood and cancer risk. *Am. J. Epidemiol.* 121:37–48
92. Sandler DP, Wilcox AJ, Everson RB. 1985. Cumulative effects of lifetime passive smoking on cancer risk. *Lancet* 1:312–15
93. Saracci R, Kogevinas M, Bertazzi P-A, Bueno de Mesquita BH, Coggon D, et al. 1991. Cancer mortality in workers

exposed to chlorophenoxy herbicides and chlorophenyls. *Lancet* 338:1027–32
94. Schreiber GH, Swaen GMH, Meijers JMM, Slangen JJM, Sturmans F. 1993. Cancer mortality and residence near electricity transmission equipment: a retrospective cohort study. *Int. J. Epidemiol.* 22:9–15
94a. Seidman H, Stellman SD, Mushinski MH. 1982. A different perspective on breast cancer risk factors: some implications of the nonattributable risk. *CA* 32:301–13
95. Shames LS, Munekata MT, Pike MC. 1994. Re: Blood levels of organochlorine residues and risk of breast cancer (correspondence). *J. Natl. Cancer Inst.* 86:1642–43
96. Smith SJ, Deacon JM, Chilvers CED, et al. 1994. Alcohol, smoking, passive smoking and caffeine in relation to breast cancer risk in young women. *Br. J. Cancer* 70:112–19
97. Stebbings JH, Lucas HF, Stehney AF. 1984. Mortality from cancers of major sites in female radium dial workers. *Am. J. Ind. Med.* 5:435–59
98. Stevens RG. 1987. Electric power use and breast cancer: a hypothesis. *Am. J. Epidemiol.* 125:556–61
99. Sturgeon SR, Schairer C, Gail M, McAdams M, Brinton LA, Hoover RN. 1995. Geographic variation in mortality from breast cancer among white women in the United States. *J. Natl. Cancer Inst.* 87:1846–53
100. Tamarkin L, Baird CJ, Almeida OF. 1985. Melatonin: a coordinating signal for mammalian reproduction? *Science* 227:714–20
101. Theriault G, Goldberg M, Miller AB, Armstrong B, Guenel P, et al. 1994. Cancer risks associated with occupational exposure to magnetic fields among electric utility workers in Ontario and Quebec, Canada, and France: 1970–1989. *Am. J. Epidemiol.* 139:550–72
102. Tokunaga M, Land CE, Yamamoto T, Asano M, Tokuoka S, et al. 1987. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki 1950–1980. *Radiat. Res.* 112:243–72
103. Tynes T, Andersen A, Langmark F. 1992. Incidence of cancer in Norwegian workers potentially exposed to electromagnetic fields. *Am. J. Epidemiol.* 136:81–88
104. US Bureau of the Census. 1942. *Sixteenth Census of the United States: 1940, Population, Vol. 1, Number of Inhabitants*. Washington, DC: US GPO
105. US Bureau of the Census. 1961. *The Eighteenth Decennial Census of the United States, Census of the Population: 1960, Vol. 1, Characteristics of the Population*. Washington, DC: US GPO
106. US Bureau of the Census. 1983. *1980 Census of the Population, Vol. 1, Characteristics of the Population*. Washington, DC: US GPO
107. US Bureau of the Census. 1992. *1990 Census of Population, General Population Characteristics, United States*. Washington, DC: US GPO
108. US Department of Energy, Energy Information Administration. 1996. *The Changing Structure of the Electric Power Industry: An Update. Rep. DOE/EIA-0562(96)*. US Dep. Energy, Washington, DC
109. US Department of Health and Human Services. 1986. *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General*. Washington, DC: US GPO. 359 pp.
110. Unger M, Kiaer H, Blichert-Toft M, Olsen J, Clausen J. 1984. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly diagnosed patients undergoing breast surgery. *Environ. Res.* 34:24–28
111. Vagero D, Ahlbom A, Olin R, Sahlsten S. 1985. Cancer morbidity among workers in the telcommunications industry. *Br. J. Ind. Med.* 42:191–95
112. Vagero D, Olin R. 1983. Incidence of cancer in the electronics industry: using the new Swedish Cancer Environment Registry as a screening instrument. *Br. J. Ind. Med.* 40:188–92
112a. van't Veer P, Lobbezoo IE, Martín-Moreno J, Guallar E, Gómez-Aracena J, et al. 1997. DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. *Br. Med. J.* 35:81–85
113. Vaughan TL, Lee JAH, Strader CH. 1993. Breast cancer incidence at a nuclear facility: demonstration of a morbidity surveillance system. *Health Phys.* 64:349–54
114. Vena JE, Freudenheim JL, Marshall JR, Laughlin R, Swanson M, Graham S. 1994. Risk of premenopausal breast cancer and use of electric blankets. *Am. J. Epidemiol.* 140:974–79
115. Vena JE, Graham S, Hellmann R, Swanson M, Brasure J. 1991. Use of electric blankets and risk of postmenopausal breast cancer. *Am. J. Epidemiol.* 134:180–85

116. Wassermann M, Nogueira DP, Tomatis L, Mirra AP, Shibata H, et al. 1976. Organochlorine compounds in neoplastic and adjacent apparently normal breast tissue. *Bull. Environ. Contam. Toxicol.* 15:478–84
117. Wells AJ. 1991. Breast cancer, cigarette smoking, and passive smoking. *Am. J. Epidemiol.* 133:208–10
118. Wertheimer N, Leeper E. 1987. Magnetic field exposure related to cancer subtypes. *Ann. NY Acad. Sci.* 502:43–54
119. Westin JB, Richter E. 1990. The Israeli breast-cancer anomaly. *Ann. NY Acad. Sci.* 609:269–76
120. Wolff MS, Collman GW, Barrett JC, Huff J. 1996. Breast cancer and environmental risk factors: epidemiological and experimental findings. *Annu. Rev. Pharmacol. Toxicol.* 36:573–96
121. Wolff MS, Toniolo PG. 1995. Environmental organochlorine exposure as a potential etiologic factor in breast cancer. *Environ. Health Perspect.* 103 (Suppl. 7):141–45
122. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. 1993. Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.* 85: 648–52
123. Wurtman RJ, Axelrod J. 1965. The pineal gland. *Sci. Am.* 213:50–60
124. Wyshak G, Frisch RE. 1982. Evidence for a secular trend in age of menarche. *N. Engl. J. Med.* 306:1033–35