

EXPERT PERSPECTIVES

Environmental Pollutants and Breast Cancer: The Evidence from Animal and Human Studies

Julia Green Brody, PhD, and Ruthann A. Rudel, MS

Clinicians are often called on by patients and the news media to comment on the environmental and preventable causes of breast cancer. Thoughtful, evidence-based comments must take into account animal and cell studies of biological mechanisms that may link chemicals from consumer products, workplace exposures, and pollution to the disease. They should also report the small but increasingly sophisticated body of epidemiologic results in humans that provide evidence of risks associated with some chemicals. Likewise, clinicians must state what we do not know. The majority of chemicals in use today have never been assessed for their roles in breast cancer, so the common statement that there is “no evidence” of a link between this disease and unstudied exposures can lead people to mistake a lack of evidence of harm for evidence of safety.

A review volume, “Environmental Factors in Breast Cancer,” published by *Cancer* this year and 2 online databases (the Mammary Carcinogens Review Database and the Epidemiology Reviews Database, accessible at www.silentspring.org/sciencereview) provide new resources for clarifying the status of scientific evidence in several key topic areas: animal studies that identify chemicals as mammary gland carcinogens¹ and epidemiologic studies of environmental pollutants,² diet (assessed prospectively),³ body size, and physical activity.⁴ This volume and the databases, both developed with support from Susan G. Komen for the Cure, include critical reviews of approximately 450 primary epidemiology research articles and information on 216 chemicals that increased the number of mammary gland tumors in animal studies.

Substantial evidence shows that increasing physical activity, avoiding weight gain and obesity after menopause, and reducing alcohol consumption contribute to lowering risk of breast cancer, and these factors are now used to support clear public health messages to reduce incidence. Less familiar are laboratory findings suggesting that environmental chemicals may influence breast cancer risk by acting as classic carcinogens that damage DNA,⁵ by hormonal mechanisms that signal tumor cells to proliferate,^{6,7} or by altering mammary gland development in early life to increase susceptibility.⁸ Epidemiologic studies have also shown evidence of increased

vulnerability to the effects of these chemicals when exposure occurs early in life and of interactions between exposure and susceptibility.^{2,9} Chemicals of concern include certain banned organochlorine compounds, air and water pollutants, organic solvents, and other ubiquitous agents, including consumer products and pharmaceuticals. These chemicals are discussed here and reviewed at length in the *Cancer* articles.¹⁻⁴

CHEMICALS THAT CAUSE MAMMARY GLAND TUMORS IN ANIMALS

In a review of databases from the International Agency for Research on Cancer, the US National Toxicology Program, the US National Library of Medicine, and other sources, Rudel and colleagues¹ compiled a list of 216 chemicals that have been associated with an increase in mammary gland tumors in at least 1 animal study, providing the most comprehensive account of known or potential mammary gland carcinogens. Nearly all of the chemicals were mutagenic, and most caused tumors in multiple organs and species, findings that are generally believed to indicate likely carcinogenicity in humans. Chemicals that have been shown to cause mammary gland tumors in animal studies include benzene, which is found in gasoline; polycyclic aromatic hydrocarbons (PAHs), which are products of combustion found in vehicle exhaust, air pollution, tobacco smoke, and charred foods; ethylene oxide, which is widely used in medical settings where women workers are routinely exposed; MX, a byproduct of drinking water chlorination; methylene chloride, a common solvent in paint strippers and glues; and pharmaceuticals, such as furosemide, griseofulvin, metronidazole, and reserpine. The new Mammary Carcinogens Review Database (www.silentspring.org/sciencereview) provides information about individual study results, chemical regulatory status, and likely sources of exposure. Fig 2 shows the 11 categories of chemicals included in the database.

Human exposure to these chemicals is likely substantial, given that 29 of them are produced in the United States at more than 1 million pounds per year, 35 are pollutants in outdoor or indoor air, 25 have affected more than 5,000 women via occupational exposure, 10 are registered with the US Food and Drug Administration as food additives, and 73 have been used in consumer products or have been potential food contaminants. In addition, 47 are pharmaceuticals and may represent a substantial exposure to individuals who use them, whereas 17 are hormones, some of which are used as pharmaceuticals. Risk assessment and regulatory documents that could become the

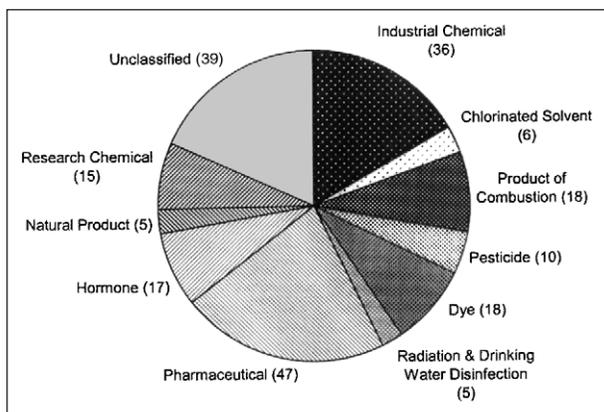


FIGURE 2.—Types of chemicals identified as mammary carcinogens. This figure shows the assignment of the 216 mammary gland carcinogens into 11 groups based on use or source. The number of chemicals in each group appears in parentheses next to the group name. (Courtesy of Rudel RA, Attfield KR, Schifano JN, Brody JG. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer*. 2007;109:2635-2666. Copyright 2007 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

basis for limiting human exposure to toxic agents have not been developed for many of the chemicals known to cause mammary tumors in animals, and the mammary gland evidence has often been ignored for chemicals that *have* been assessed. For example, the US Environmental Protection Agency has developed estimates of human carcinogenic potency for only 20 of the 216 chemicals that have been associated with mammary gland tumors in animals; and although the Occupational Safety and Health Administration requires medical surveillance for workers exposed to 11 of the 216 chemicals, mammography is not one of the tests required.

HORMONALLY ACTIVE CHEMICALS

Currently, there is no comprehensive reference identifying chemicals shown in laboratory studies to affect the endocrine system—often referred to as endocrine-disrupting chemicals (EDCs)—nor any routine screening of chemicals to determine whether they are EDCs. However, research shows that conditions of pregnancy that affect the hormonal environment of the developing fetus (eg, birth weight and length, maternal age, twin membership, diethylstilbestrol exposure) are associated with the offspring's breast cancer risk in adulthood, supporting the hypothesis that in utero exposure to EDCs could also affect breast cancer risk.¹⁰ In animal models, in utero exposures to certain EDCs (eg, dioxin, the herbicide atrazine, and the Teflon-related chemical perfluorooctanoic acid) have been shown to affect mammary gland morphologic parameters, such

as the timing and extent of differentiation of terminal end buds and ductal branching as well as tumor incidence following treatment with a carcinogenic chemical.⁸ These effects on the developing mammary gland are not evaluated in chemical screening programs at this time; however, this is a critical topic for future research. In addition, evidence that hormone replacement therapy and higher levels of endogenous estrogens increase breast cancer risk closer to the time of diagnosis illustrate another mechanism by which estrogen-like EDCs may play a role in breast cancer, given that everyday consumer products contain chemicals shown to act like estrogen in laboratory studies, for example by causing increased uterine weight in animal studies and stimulating growth in cultured human breast cancer cells. Although many of these estrogen mimics are less potent than estradiol, laboratory evidence has demonstrated that exposures must be considered cumulatively because the compounds act additively.¹¹

HUMAN EVIDENCE

Epidemiologic studies of breast cancer and environmental pollutants have focused almost exclusively on a small handful of persistent organochlorine pesticides. Studies of these pollutants began in the early 1990s and relied primarily on blood measurements in adults, typically after diagnosis and decades after the chemicals were banned from use.¹² The results were overwhelmingly negative, leading many to the overgeneralized conclusion that environmental pollutants do not contribute to breast cancer. However, newer studies that consider more complex causal models, taking into account variables such as genetic susceptibility, exposure in early life, and younger age at diagnosis, have produced more coherent evidence of the associations between certain chemicals and breast cancer.^{2,9}

In a review of the literature by Brody and associates,^{2,4} studies of polychlorinated biphenyls (PCBs—used in electrical equipment and other consumer products until they were banned in the United States in the 1970s) showed 2- to 4-fold increases in breast cancer risk among women who experienced high exposure to this agent and who also had the CYP1A1 m2 genetic variant, which affects the metabolism of PCBs, steroid hormones, and PAHs. One study found the effect in premenopausal patients, and the other 3 found it in postmenopausal patients. This is an unusually consistent set of findings, considering the general lack of consistency in gene-environment epidemiologic studies.

In a remarkable recent study that demonstrated increased breast cancer risk associated with DDT exposure in young women, Cohn and colleagues⁹ used stored blood drawn from 1959 to 1967, the peak years of exposure to this agent in the United States. The study, which was the first to use a relevant measure of DDT exposure, is a reminder that women with lifetime exposures to the post-World War II synthetic organic

chemicals are still relatively young for breast cancer diagnoses, so the effects of early-life exposure to these chemicals continue to unfold. Similarly, the most recent report on dioxin exposure after the 1976 Seveso accident, showed a higher risk among women who were infants to 40 years old at the time.

Likewise, evidence is mounting for a role of PAHs in breast cancer. Most although not all studies of PAHs and air pollution report a high risk for breast cancer associated with exposure to these carcinogens, particularly in studies of exposure or diagnosis at younger ages. The Long Island Breast Cancer Study reported a 48% higher risk in women under age 65 years who had PAH-DNA adducts in their blood than in women with no PAH-DNA damage.¹³ Efforts to understand the relationships with genetic polymorphisms that affect cell repair, detoxification, and other mechanisms are underway.

Despite these positive findings, overall, the epidemiologic literature on environmental pollutants and breast cancer remains sparse, and the studies are vulnerable to exposure misclassification and confounding, so multiple investigations of suspect exposures will continue to be important.

PUBLIC HEALTH IMPLICATIONS

Research on environmental pollutants and breast cancer has not reached maturity; but the results of animal and cell line studies have clearly indicated that some common chemicals cause mammary gland tumors, promote tumor growth, and result in cancer susceptibility in offspring exposed prenatally, providing evidence that these chemicals might play a role in human breast cancer. Limited epidemiologic evidence suggests 50% to 500% increases in risk in subgroups of women exposed to pollutants such as PCBs, DDT, PAHs, and chemical solvents. Because breast cancer is so common and is the leading cause of death in relatively young women (late 30s to early 50s), protective public health policies should include interventions to reduce exposure to suspect chemicals, many of which, such as PAHs, have other known adverse health effects.

It is time to begin talking about air pollution as a possible breast cancer issue, to develop requirements for screening new chemicals before they come into widespread use, and to support individuals who seek to reduce their own exposures. Although we are tempted by the desire to be reassuring when asked about the potential role of consumer product chemicals in breast cancer, an evidence-based response to this question can only support additional research and precautionary measures to reduce exposure.

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