

The Ecology of Breast Cancer

*The promise of prevention
and the hope for healing*

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Environmental chemicals, contaminants, and breast cancer

Chapter Summary

More than 75 years ago, scientists began using coal tar derivatives to induce mammary gland cancer in laboratory rodents in order to investigate the process of carcinogenesis and hormone dependency of certain tumors. This animal model has been in widespread use ever since, but more general research into the role of environmental chemicals in the origins of breast cancer has been slow to develop.

Early studies of environmental chemicals and breast cancer in humans dealt exclusively with exposures in adults. But, recent developments have firmly established the importance of adopting a life-course perspective when looking for the origins of breast cancer, including those related to chemical exposures. For example, combination hormone replacement therapy after menopause is associated with increased breast cancer risk within a few years, while diethylstilbestrol exposure *in utero* increases breast cancer risk decades later. A life-course perspective makes epidemiologic studies of environmental chemicals particularly challenging because of difficulty establishing an exposure history and variable latency periods between relevant exposures and breast cancer diagnosis.

A variety of mechanisms are probably involved in chemical carcinogenesis in the breast. Endocrine disrupting chemicals can alter breast development, tissue structure, and hormone responsiveness, increasing susceptibility to cancer years later.¹ They may promote early stages of cancer, long before it is clinically apparent. Environmental chemicals or their metabolites can directly damage DNA, alter gene expression, influence the cell cycle, cellular proliferation, and programmed cell death. They can also modify the immune response to cancer.

Studies of workplace-related chemical exposures and breast cancer risk are inadequate and historically relatively uncommon. Now it appears increasingly likely that workplace exposures to known or suspected carcinogens and endocrine disrupting chemicals can increase the risk of breast cancer. Specific occupations, including chemical, rubber, plastics, and textile manufacturing, agriculture, and nursing deserve urgent attention.

Rodent studies are relevant for evaluating risks to humans because the biological processes involved in mammary gland growth, differentiation, development, and response to environmental stimuli are similar. By enabling better understanding of risk factors for breast cancer and their mechanisms of action, rodent studies can help to identify opportunities for breast cancer prevention. A recent literature review using data from the National Toxicology Program, the International Agency for Research on Cancer (IARC), the Carcinogenic Potency Database, and the Carcinogenesis Research Information System identified 216 chemicals associated with increases in mammary gland tumors in at least one well-conducted animal study.² They include industrial chemicals, products of combustion, pesticides, dyes, drinking water disinfection byproducts, pharmaceuticals, hormones, and research chemicals. Most of these have been classified by IARC as carcinogenic, probably carcinogenic, or possibly carcinogenic to humans. Unfortunately, human epidemiologic studies of these chemicals, some of which are commonly encountered in food, air, water, or consumer products, are extremely limited or non-existent.

According to a report from the Institute of Medicine, the strongest evidence of chemically-related increased breast cancer risk in humans comes from studies of combination hormone therapy products, current use of oral contraceptives, alcohol consumption, and tobacco smoking.³ Evidence linking passive smoking, other organic solvents, ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), 1,3 butadiene, and some agricultural chemicals to breast cancer is not as strong but increasingly persuasive (see box 5.2).

Other chemicals that alter mammary gland development and are associated with evidence of increased cancer risk in animal studies include bisphenol A, cadmium, perfluorinated compounds, dioxins, and atrazine.

In a 2011 paper from IARC, “Preventable Exposures Associated with Human Cancers,” the authors note that every agent known now to be carcinogenic to humans “can be considered to represent cancers that might have been prevented had scientists been able to predict cancer hazards earlier or had public health authorities been willing to act more quickly when scientific information became available.”⁴

Therein lies a challenge. When do we know enough to act and who should decide? Randomized controlled trials of the effects of non-pharmaceutical chemicals on breast cancer risk will never be available. Even well-designed prospective epidemiologic studies with accurate exposure assessment and long-term follow up cannot provide meaningful data for decades. Moreover, it is exceedingly difficult to tease out

the effect of chemicals within the noisy variability of hormones, other environmental exposures, diet, exercise, stress, and other biologic and social factors.

Although understanding the role of environmental chemicals in the origin of breast cancer will always be limited by research challenges, that need not keep us from taking action to minimize risk, based on what we know. Despite uncertainties and data gaps, individuals, health care providers, public health officials, and policy makers have multiple opportunities to intervene throughout the life course, based on sound, early warnings and firmly established evidence, to reduce exposures to hazardous chemicals with the goal of preventing breast cancer.

A brief history of environmental chemicals and breast cancer

More than 200 years ago Percival Pott, a London surgeon, recognized that chimney sweeps can develop scrotal cancer from exposure to soot laden with polycyclic aromatic hydrocarbons (PAHs). This was the first time that an environmental chemical cause of cancer was identified. It raised new questions about the origins of cancers in other organs. Many years later, in the 1930s, studies showed PAHs could also cause mammary gland cancer in laboratory animals.

PAHs occur naturally in coal and crude oil. They are common environmental pollutants formed by the incomplete combustion of fossil fuels and wood. Coal tar sealants, creosote, and asphalt have high concentrations of PAHs. Traffic-related air pollution and cosmetics made of coal tar contain PAHs. Barbecuing, smoking, or charring food over a fire produces PAHs.

Among the PAHs, 3,4-benzopyrene (BP); 3-methylcholanthrene (MCA); 2-acetylaminofluorene (2-AAF); and 7,12 dimethylbenzanthracene (DMBA) are most widely studied. DMBA is more efficient than the others in inducing mammary cancer in susceptible strains of animals, and the DMBA model is still widely used in research after more than 75 years. It is sometimes called the Huggins model, named after Nobel prize-winning cancer biologist Charles Huggins, who used it to investigate the hormone-dependency of various cancers, including in the breast.⁵

Huggins realized that the chemical acted within a context that influenced its ability to cause cancer. He sometimes called this context “the soil,” metaphorically comparing soil nutrient requirements for seed germination and plant growth to a susceptible host environment for cancer initiation and growth. Huggins and many others since have shown that the hormonal

environment, along with dietary manipulations at various times, can strongly influence the capacity of DMBA to cause mammary tumors and their progression.⁶

Among the features of DMBA-induced mammary tumors:⁷

- The timing of exposure to DMBA strongly influences its potency; a single oral dose at 50 days of age can induce mammary tumors in nearly 100 percent of susceptible rodents, whereas earlier or later exposures are less effective.
- Sprague Dawley rats fed a diet consisting of 20 percent corn oil (high omega 6:3 fatty acid ratio) from weaning are much more susceptible to developing mammary gland cancer after exposure to the carcinogen DMBA than animals fed a low fat diet exposed to the same carcinogen.⁸
- Pre-pubertal dietary omega 3 fatty acids can help to protect against DMBA-induced mammary tumors in laboratory rodents, but exceptionally high levels of this kind of fat (39% of total calories) can actually promote mammary cancer development.⁹
- DMBA tumors are hormonally responsive. Reducing prolactin levels, removing the ovaries, or treating with testosterone causes the tumors to regress. Moderate doses of estrogen or progesterone treatments stimulate their growth, as does insulin. High doses of estrogen can cause DMBA-induced tumors to regress

Although rodent strains differ in their susceptibility, most scientists agree that the DMBA model is relevant for studying the origins of human breast cancer¹⁰ (see box 5.1). But, despite decades of experience using this chemical to cause mammary cancer in laboratory animals, the notion that other environmental chemicals could increase breast cancer risk in humans has been slow to gain traction—probably for several inter-related reasons.

First, breast cancer has always been predominantly seen as a quintessential hormone-related malignancy. In the late 19th century, Scottish surgeon George Beatson reported that removal of the ovaries in several of his patients caused the remission of inoperable breast cancer.^{11,12} Then various hormones, including estrogen, were isolated and characterized.¹³ In 1932, Lacassagne induced mammary cancer in male rodents with estrone, stimulating more research into endocrine carcinogenesis.¹⁴ Many studies show that higher lifetime exposure to estrogen is a predictor of breast cancer risk.

Thus, from the beginning, breast cancer research has been dominated by investigating the roles of endogenous estrogen and other hormones. Relatively recently, however, a long and growing list of chemicals present in the ambient environment or in consumer products have been shown to have hormone-like activity or otherwise disrupt hormone function. The role of these endocrine disruptors in the development of breast cancer is now gaining increased attention.

Second, an appreciation of the importance of a life course perspective for understanding the origins of breast cancer is relatively new. In the 1970s, the recognition that fetal exposure to diethylstilbestrol (DES) could cause reproductive tract malignancies in humans decades later stimulated entirely new avenues of research.¹⁵ Animal studies show that developmental exposures to endocrine disrupting compounds can alter tissue architecture, hormone recep-

Box 5.1: Evolution of animal testing

Scientists have used laboratory animals to study the cancer-causing properties of chemicals since early in the 20th century. In the U.S., the process became more standardized at the National Cancer Institute in the 1960s and further developed at the National Toxicology Program beginning in 1978. Carcinogenic assays generally utilize two or three dosage levels of the test chemical over two years in adult rats and mice. Along with PAHs, ethylene oxide, methylnitrosourea, butylnitrosourea, ethylnitrosourea, and urethan were among the first chemicals identified as mammary carcinogens in laboratory mice.^{16,17} By 1991, the National Toxicology Program had reported that 198 of 379 chemicals were carcinogenic in at least one of four long-term experiments. Among them, 27 chemicals were positive and seven chemicals equivocal for causing mammary gland cancer.¹⁸ These findings added to the growing concern that exogenous chemicals might be contributing to the rising incidence of breast cancer in the general population.

A recent literature review using data from the National Toxicology Program, the International Agency for Research on Cancer, the Carcinogenic Potency Database, and the Carcinogenesis Research Information System identified 216 chemicals associated with increases in mammary gland tumors in at least one well-conducted animal study.¹⁹ They include industrial chemicals, products of combustion, pesticides, dyes, drinking water disinfection byproducts, pharmaceuticals, hormones, natural products, and research chemicals. Of these, 73 have been present in consumer products or as contaminants of food, 35 are air pollutants, 29 are produced at more than one million pounds per year in the United States, 35 are air pollutants, and 25 have involved occupational exposures to more than 5000 women. Nearly all of the chemicals can cause DNA mutations and most caused tumors in multiple organs and species. These features mean that they are also likely to cause cancer in humans. Unfortunately, few of these chemicals have been studied as causes of breast cancer in epidemiologic studies.

Rodents continue to be used because the biological processes involved in mammary gland growth and differentiation are similar to humans. Scientists are now more systematically investigating the effects of environmental chemicals on mammary gland development and subsequent cancer risk in laboratory animals, but new protocols have not yet been incorporated into assessments used for regulatory purposes.²⁰ Nonetheless, it is increasingly clear that critical windows of vulnerability to chemical and other environmental exposures occur prenatally and in infancy, puberty, and pregnancy, influencing the risk of mammary gland cancer.²¹

tors, hormone responsiveness, gene expression, and various biologic set points, increasing cancer susceptibility in adulthood.²² Now we know that developmental exposure to DES and probably the pesticide DDT increase breast cancer risk in humans as well.^{23,24} Widespread early-life exposures to other endocrine disrupting chemicals are a growing concern.

Third, with few exceptions, human evidence for chemical carcinogens identified by the International Agency for Research on Cancer (IARC) or the EPA comes primarily from occupational studies. The large majority of these were conducted when most employees in industry were men. Thus, the likelihood of identifying breast carcinogens in the workplace, should they exist, was initially extremely low. A few early occupational studies reported no excess of breast cancer-related deaths in workers exposed to various industrial chemicals. As a result, for a long time scientists and public health officials interested in breast cancer saw little reason to look more closely at environmental chemicals.^{25,26,27}

Finally, studying the potential role of environmental chemicals in breast cancer causation poses many challenges:

- Breast cancer is not a single disease but rather a collection of different diseases with different etiologies. Environmental chemicals are likely to play a more important role in some than in others.
- The biologic effects of chemicals depend on timing, duration, and magnitude of exposure, and establishing an exposure history is often very difficult. Individuals usually do not know and cannot report their exposure to environmental chemicals in the ambient environment. Exposures in the workplace and from consumer products are usually poorly characterized. Job histories, residential location, and biomonitoring can add useful information, but each has limits. The long latency of breast cancer makes it particularly difficult to overcome these challenges.
- Epidemiologic studies must deal with various kinds of bias and confounding. Interactions among chemicals, nutrition, other behavioral factors, genetic background and social circumstances create a complexity that is difficult to disentangle and understand. Individual differences in metabolism of environmental chemicals and differences in susceptibility due to underlying contextual features are likely to be important in various subgroups, but these will be obscured in analyses of larger populations.

Early Occupational studies

Studies of breast cancer risk associated with occupational chemical exposures did not begin to appear in the medical literature until the 1970s. A report from the UK found that sin-

gle women hair-dressers had higher than expected deaths from breast cancer during 1959-1963.²⁸ Data related to married hair-dressers were lacking because they were classified according to their husbands' occupations, leaving many women out of the analysis. These findings led to a number of cohort and case-control studies of varying design and length of follow up that attempted to determine if regular exposure to hair dyes increased the risk of breast cancer.

Laboratory studies (the Ames test) had shown that many hair dyes were mutagenic. They contained aromatic amines or aromatic nitroso compounds that might be implicated in increased breast cancer risk. Moreover, many hair sprays were aerosolized initially with vinyl chloride²⁹ and then methylene chloride, until banned from this use by the FDA in 1989.³⁰ Both vinyl chloride and methylene chloride are mammary gland carcinogens in rodents.³¹

A recent evaluation of the literature by the IARC found that hair dyes are probably carcinogenic in hairdressers and barbers. Most, although not all, studies of breast cancer specifically found no association.³² A 2005 meta-analysis of studies from 1966-2005 found no increased risk of breast cancer with the personal use of hair dyes, although the risk of blood-related malignancies was slightly increased.³³

This issue is complicated by changes in the formulations of hair dyes beginning in the 1980s as some manufacturers moved away from more obviously carcinogenic chemicals after concerns became public. Nonetheless, a recent study reports more evidence of DNA damage in breast ductal epithelial cells in breast milk of women who use hair dyes compared to those who do not.³⁴ A report from a committee convened by the Institute of Medicine concluded "current personal use of hair dyes is unlikely to be an important risk factor for breast cancer."³⁵

After the initial report related to hair dyes, additional occupational studies of other chemical exposures and breast cancer risk occasionally began to appear. One found excess breast and urinary tract cancer mortality among white women working in seventeen companies engaged in polyvinyl chloride (PVC) fabrication.³⁶ Soon after, a cluster of cancer in women was reported in a Swedish factory where workers wrapped bearing rings that were covered with anti-rust oil. Findings included excess mortality from cancer of the uterus, ovary, breast, thyroid, brain, colon, and bladder.³⁷ The authors suspected that N-phenyl-1-naphthylamine, an anti-oxidant in the oil, or one of its derivatives was likely to be responsible.

An apparent cluster of breast cancer in women working in a coiling and wire-drawing area of a lamp manufacturing department of Canadian General Electric prompted a study of all women who had worked there for at least six months and long enough before to account for the latency of cancer development.³⁸ They found a significantly increased risk of breast and

other gynecological cancers in women who worked in the area where they had been exposed to the solvents methylene chloride and trichloroethylene.

Beyond the workplace: The evolution of epidemiologic studies in women

Support for a closer look at the role of exogenous carcinogens in the origins of breast cancer in the general population grew with reports of chemicals regularly detected in breast milk. Although the pesticide DDT and its residues had been detected in breast milk as early as the 1950s, newer studies showed additional fat-soluble chemical contaminants, including polychlorinated biphenyls (PCBs) and the pesticides dieldrin, chlordane, and heptachlor. Some of these chemicals were carcinogenic in animal testing, and they were known to concentrate in fat tissue.³⁹ DDT was reported to promote PAH-induced mammary gland cancer in male rats.⁴⁰

New technologies also enabled scientists to measure metals in breast tissue and breast milk.⁴¹ Despite the prevailing view that endogenous hormones were largely responsible for breast cancer patterns, some scientists and public health advocates were increasingly concerned that exposures to exogenous environmental agents were wrongly being ignored.

Results of initial studies of organochlorine chemical residues in fat tissue or blood from women with and without breast cancer were inconsistent. One showed no difference in levels of these chemicals⁴² while others showed higher levels of PCBs, DDT, and DDE^{43,44} and beta-hexachlorocyclohexane (HCH)⁴⁵ in women with breast cancer.

A report from Israel found decreasing population-wide exposures to organochlorines in milk associated with a reduction in breast cancer mortality, adding support to the hypothesis that they might be causally related.⁴⁶ Participants in a workshop convened at the International Society of Environmental Epidemiology discussed whether organochlorine compounds might contribute to breast cancer risk by altering estrogen production or metabolism.⁴⁷ A 1992 review and commentary summarized experimental and epidemiologic evidence that some organochlorines have estrogenic properties and are often, though not always, present at higher levels in women with breast cancer.⁴⁸

The emergence of a life-course perspective

In the late 1980s, new evidence showed that higher exposure to estrogens in the prenatal period was associated with increased breast cancer risk.^{49,50} This suggested that prenatal imprinting could alter the trajectory of breast development and create vulnerability, perhaps through priming estrogen receptor responses later in life. Although the initial focus was on estrogen levels, the possibility that early life exposures to other agents could also influence

breast cancer risk decades later began to get attention.⁵¹ After all, it was already known that prenatal exposure to radiation increased the risk of leukemia in children, and intrauterine exposure to diethylstilbestrol (DES) could cause vaginal adenocarcinoma in young girls and women. More recent studies show that fetal exposure to DES also increases the risk of breast cancer in women.^{52,53,54}

Epidemiologist Nancy Krieger pointed out that after decades of research, known risk factors accounted for only about one-third of breast cancer cases in the U.S.⁵⁵ Krieger and others proposed combinations of exposure to exogenous carcinogens and biologic susceptibility—both of which are influenced by social conditions—as a way of explaining breast cancer patterns and its social gradients.⁵⁶ This might help explain why African-American women are at higher risk of breast cancer than white women before age 40 but at lower risk after that.

A life-course perspective proposes that determinants of breast cancer risk begin early in life when rapidly dividing ductal cells are more vulnerable to DNA damage than cells at rest. After puberty, monthly fluctuations in breast cell growth related to the menstrual cycle would sustain susceptibility to various exposures, including endogenous hormones that could promote the growth of cells or tissues that had been initiated on pathways toward cancer by exogenous agents. An early full term pregnancy would result in more complete differentiation of breast tissue, making it ultimately less vulnerable to malignant transformation. This, Krieger said, “implies that the presumed joint determinants of breast cancer incidence—exposure and susceptibility—cannot be examined statically, but instead must be considered in relation to each other at every stage in a woman’s life.”

Several lines of evidence support the idea that early-life chemical exposures can increase breast cancer risk. A 2001 review of epidemiologic studies concluded that most well conducted, well controlled epidemiologic studies looking at exposures in adults did not find a significant correlation between body burdens of DDT or DDE and breast cancer risk.⁵⁷ Similarly, results of studies of body burdens of dieldrin and breast cancer risk were inconsistent. In 2007, however, scientists gained access to blood samples that had been collected from a group of women much earlier in their lives and stored for later analysis. They averaged 26 years of age when blood was collected. In this group, high levels of serum DDT were associated with a significant 5-fold increased risk of breast cancer among women who were born after 1931.⁵⁸ These women were under 14 years of age in 1945, when DDT came into widespread use, and mostly less than 20 years old as DDT use peaked. This study clearly supported the hypothesis that early life chemical exposures may influence breast cancer risk even more than adult exposures. This finding is similar to evidence that breast cancer risk is higher with radiation exposures earlier in life compared to later in adulthood.

More recently, a study using stored serum identified a six-fold increased risk of breast cancer before age 50 in women with higher levels of a certain kind of polychlorinated biphenyl

(PCB 203) measured shortly after giving birth.⁵⁹ Because PCBs are persistent, it can be assumed that the levels were similar during pregnancy and probably during puberty.

Another intriguing observation comes from studies of the influence of birth order on breast cancer risk. When the *in utero* origin of breast cancer was first proposed, most attention focused on the hormonal environment within the uterus. Studies showed that estrogen levels were higher in first pregnancies than in those that followed, leading to speculation that breast cancer risk might differ by birth order and be higher women who had been first-born.⁶⁰ A 1991 study using data collected in the 1960s from three countries with high, medium, and low breast cancer incidence found reduced risk of pre-menopausal breast cancer in women who were not first-born but statistically significant only for those second-born. (RR= 0.71)⁶¹ Since then, the results of other studies have been inconsistent.

A recent report finds that birth order is more strongly associated with breast cancer risk when breastfeeding was taken into account. In this population-based case-control study, being born later was associated with much lower breast cancer risk among breastfed women (OR=0.58) who have three or more older siblings compared to first-born women.⁶² But, this was not the case among non-breastfed women, suggesting that something in addition to higher estrogen levels in first pregnancies may influence breast cancer risk.

Breast feeding lowers maternal levels of persistent, fat soluble chemicals that build up over time by off-loading them to a nursing infant. Thus, fetuses and infants borne in subsequent pregnancies will be exposed to lower levels. Breast fed first-born children will not only be exposed to higher estrogen levels but also to higher levels of contaminants *in utero* and during breast feeding, which may help explain a higher breast cancer risk than in siblings born later.

In their recent report “Breast Cancer and the Environment: A Life Course Approach” a committee convened by the Institute of Medicine has fully endorsed the importance of adopting a life-course perspective for understanding the origins of breast cancer and breast cancer risk.⁶³ Endocrine disrupting chemicals are particularly of rapidly growing interest. Hormones and other signaling molecules are critically important mediators of development in cells, tissues, organs, and whole biologic systems. Small changes in hormone levels or function during development can alter tissue architecture, gene expression, and biochemical set points, with consequences for disease risk many years later.

Animal studies showing the influence of early-life exposures to environmental chemicals on mammary gland development and subsequent cancer risk make clear the challenges facing epidemiologists who seek to study the impacts of chemicals on breast cancer risk in humans. In general, estimating developmental exposures to non-persistent chemicals and following a cohort of women for decades in order to assess breast cancer risk is difficult

and expensive. Some large cohort studies have assessed certain early life variables, such as birth weight, height, breast feeding, and childhood nutrition, but none has been designed to measure or estimate exposure to non-persistent environmental chemicals, with the exception of DES, intentionally administered as a pharmacologic agent to pregnant women. The increased breast cancer risk associated with fetal exposure to DES and higher exposure to DDT before age 14 show that developmental exposures are important in humans, as they are in laboratory animals.

Recent epidemiologic studies of environmental chemicals and breast cancer

In 2007, scientists from the Silent Spring Institute published a review of epidemiologic studies of chemicals and breast cancer, with an emphasis on those published within the previous five years.⁶⁴ Based on a relatively small number of studies, they concluded that evidence supported an association between breast cancer and PAHs as well as polychlorinated biphenyls (PCBs) in conjunction with certain genetic profiles that influence hormone metabolism and carcinogen activation. Some but not all studies show an increased risk of breast cancer with higher levels of exposure to pesticides.

A recent population-based case control study in France⁶⁵ found modest increases in breast cancer risk that may be related to exposure to occupational carcinogens among nurses, textile workers, rubber and plastics product makers, and in women employed in the manufacture of chemicals and non-metallic mineral products.

This study in France found a decreased incidence of breast cancer among women in agriculture, as has also been reported in other European studies.^{66,67} In some countries, however, including the U.S. and Canada, increased breast cancer risk is reported in female farmers associated with some pesticide exposures.^{68,69} These discrepancies may be explained by differing agricultural practices and pesticide use in various countries.

A recent population-based case-control study in Canada found a greater than four-fold increased risk of pre-menopausal breast cancer in women employed in the automotive plastics industry.⁷⁰ Metal working, food canning, and agricultural work were also associated with significantly increased risk. The authors of this study noted that women are often exposed to a “toxic soup” of chemicals in these occupations, including known or probable carcinogens and endocrine disruptors, such as phthalates, bisphenol A, and flame retardants.

Nurses are at increased risk of breast cancer as well.^{71,72,73} They may be exposed to ionizing radiation, chemotherapeutic agents, and ethylene oxide. They may also have worked rotating night shifts and been exposed to excessive light at night, which increases breast cancer risk (see chapter 6).^{74,75,76}

Specific chemicals and breast cancer

Endocrine disrupting compounds

Endocrine disrupting compounds (EDCs) interfere with hormone functions through a variety of mechanisms. They may mimic or block the action of hormones, interfere with hormone synthesis, metabolism, or excretion, alter the concentration of hormone receptors, or interfere with gene transcription after a hormone-receptor complex has attached to response elements on DNA. Early-life exposures to EDCs are of particular concern because they can alter the trajectory of developmental processes with long-term consequences.^{77,78}

In animal studies, prenatal or early postnatal exposure to some endocrine disrupting chemicals causes permanent changes in mammary gland development, altering their susceptibility to cancer-causing environmental agents later in life. Recently, Fenton et al. reviewed much of this research.⁷⁹ Examples of chemicals that can modify mammary gland development and influence subsequent breast cancer risk in laboratory animals and in humans, if data are available, include:

Diethylstilbestrol (DES)

Diethylstilbestrol is a synthetic estrogen given to some women during pregnancy in the 1950s through the early 1970s. Its purpose was to minimize the risk of miscarriage, despite the lack of evidence that it was effective. *In utero* exposures were first shown to be associated with increased risk of cancer of the female reproductive tract and more recently, breast cancer.⁸⁰ Laboratory rats exposed around the time of birth to 1-2 µg of DES have an increased susceptibility to mammary gland cancer after later treatment with DMBA.⁸¹ *In utero* DES exposure probably increases cancer susceptibility by slowing mammary gland maturation.⁸² The most mature structures of the mammary gland, lobules, are most resistant to developing cancer after exposure to chemical carcinogens, while terminal end buds are more susceptible. Prenatal DES exposure increases the number of terminal end buds. Permanent re-programming of gene expression, through epigenetic mechanisms, is likely to be involved.

Bisphenol A

Bisphenol A (BPA) is a chemical that can be polymerized to make polycarbonate plastic. Unpolymerized BPA can leach from polycarbonate food or beverage containers contaminating what people eat and drink. Bisphenol A is also a component of epoxy resins lining most food and beverage cans. Food and beverages contaminated with BPA are a major source of human exposures. A more-recently discovered route of exposure comes from handling printed receipt papers that are coated with BPA.⁸³ In fact, many paper products contain BPA and are

likely to result in exposure through the skin.⁸⁴ According to the Centers for Disease Control and Prevention, over 90 percent of Americans have measureable BPA and its metabolites in their urine.

Considerable scientific debate centers on the extent to which BPA exposures are rapidly metabolized into an inactive form and excreted.^{85,86} This is an exceedingly important issue because human exposures to BPA are ubiquitous. A large and rapidly growing body of experimental evidence shows diverse adverse effects of BPA, often after exposures similar to those experienced in the general population.⁸⁷ This is not a circumstance in which professionals charged with protecting the public's health want to be wrong.

Most efforts to restrict BPA in consumer products have focused on exposures in infants and children. Recently, the Food and Drug Administration withdrew authorization to use BPA in infant formula packaging, based on packaging manufacturers' earlier decision to voluntarily stop using it for that purpose rather than an agency determination that the use is unsafe.⁸⁸

Evidence that free, active bisphenol A has been measured in amniotic fluid, umbilical cord blood, and the livers of human fetuses is unaddressed by this decision.^{89,90,91,92,93} Efforts to protect infants and children from exposure to BPA are laudable, but the developing human fetus is also directly exposed to the active compound. Reducing or eliminating exposures in adults as well is the only way to address that critical time window of vulnerability.

Bisphenol A is a relatively weak estrogenic agent as measured by its affinity for the classic estrogen receptor. But, BPA has a number of other biologic activities, including interacting with at least three other non-classic estrogen receptors with even higher affinity than endogenous estrogen.⁹⁴ It can also act as an androgen receptor antagonist and interact with the thyroid hormone receptor.

Studies linking Bisphenol A and breast cancer include:

- In mice, maternal exposure to low levels of BPA administered beneath the skin during the second half of pregnancy and for several days after birth caused an increased number of terminal end buds (TEBs) in the mammary glands, a decreased rate of apoptosis in the TEBs, an increased percentage of cells expressing the progesterone receptor (PR) in the mammary gland, increased lateral branching, and pre-cancerous changes.^{95,96} These changes increase the risk of mammary gland cancer in adult female animals.
- In Wistar rats, with gestational exposure alone, BPA increases the number of terminal ducts, TEBs, alveolar buds, and pre-cancerous lesions in the mammary gland.⁹⁷ Prenatal exposure to BPA (via maternal subcutaneous dosing), coupled

to a sub-carcinogenic dose of N-nitroso-N methylurea (NMU), resulted in an increased percentage of cancers in the mammary gland.⁹⁸

- In Wistar rats, maternal exposure to low levels of BPA administered beneath the skin during pregnancy induces excessive cellular growth in mammary gland ducts and pre-cancerous lesions in female offspring.⁹⁹
- In Sprague-Dawley rats, subcutaneous maternal exposure to BPA at 250 microgms/kg/day resulted in serum levels of active and inactive BPA similar to what has been measured in humans.¹⁰⁰ Occasional female offspring exposed at this level during gestation and lactation developed mammary gland cancer beginning at post-natal day 90 in the absence of any additional carcinogen exposure although the incidence was not statistically significant. The authors concluded that BPA may act as a complete mammary gland carcinogen.

These studies are sometimes criticized because the BPA was administered by injection rather than via the gastrointestinal tract. Oral administration, some people argue, would more closely mimic human dietary exposures and allow more rapid metabolism of BPA into the inactive compound in the liver after intestinal absorption. Administration of the chemical by injection bypasses the detoxifying liver allowing longer exposure to the active compound—a scenario many conclude is irrelevant for assessing human risks.

While the argument has some merit, it comes up numerous human studies documenting significant blood levels of free, active BPA.¹⁰¹ These studies challenge the model of rapid BPA metabolism and excretion. Significant human exposures to BPA may also occur through the skin or through the mucous membranes of the mouth—pathways that also bypass rapid liver metabolism. Nonetheless, a number of experimental studies have used oral dosing as the exposure route.

- In Sprague-Dawley rats, early postnatal oral maternal exposures to a low (25 microgm/kg) and high (250 microgm/kg) daily dose of BPA from day two postpartum until weaning caused a dose-dependent increase in mammary gland cancer in offspring subsequently treated with DMBA.^{102,103} Maternal gestational and lactational exposures to orally administered BPA also shift the window of susceptibility to DMBA carcinogenesis and alter levels of proteins related to cell proliferation, including estrogen and progesterone receptors, in the mammary glands of offspring.¹⁰⁴
- In mice, oral maternal exposure to BPA at 25 microgm/kg/day and 250 microgm/kg/day during gestation resulted in increased susceptibility to DMBA-induced

mammary gland cancer in female offspring.¹⁰⁵ There was no effect of the lower dose on mammary gland morphology, despite increased cancer risk.

- In rhesus monkeys, BPA administered orally (400 microgm/kg/gestational day 100-165 of pregnancy) advanced development of the mammary glands in female offspring and resulted in more buds per ductal unit compared to controls.¹⁰⁶ The dose resulted in serum levels of unconjugated, active BPA similar to levels measured in humans.

Taken together, these findings show that environmentally-relevant exposures to BPA alter development of the mammary gland in mice, rats, and monkeys. Whether administered by injection or orally, the chemical increases susceptibility to and the risk of mammary gland cancer in later life. No epidemiologic studies have explored the impacts of fetal, infant, or childhood BPA exposures on breast development and breast cancer risk in humans.

Parabens

Parabens are a family of related compounds that includes esters of p-hydroxybenzoic acid. They were first introduced as preservatives in pharmaceutical products in the 1920s, but are now used in other applications.¹⁰⁷ Various forms of parabens — methyl-, ethyl-, propyl-, butyl-, and isobutyl-paraben — serve as preservatives in an array of foods, cosmetics, and pharmaceuticals.¹⁰⁸

Parabens have estrogen-like properties in cell cultures, causing proliferation of estrogen-responsive cells, although they are thousands of times less potent than naturally-occurring estrogen in this regard.^{109,110} However, studies also show that parabens alter gene expression in estrogen responsive cells in patterns that differ from naturally-occurring estrogen.¹¹¹ Thus, parabens could plausibly have biologic effects not predicted solely by the potency of their ability to activate the estrogen receptor and cause cell proliferation.¹¹² Some parabens also have anti-androgenic properties.¹¹³

In 2003, scientists proposed that parabens in underarm deodorants and antiperspirants could be absorbed through the skin and might be related to increased risk of breast cancer, particularly since tumors disproportionately occur in the upper outer quadrant of the breast.¹¹⁴ Parabens have also been detected in breast cancer tissue after surgery, at concentrations sufficient to stimulate proliferation of MCF-7 breast cancer cells in cell cultures.^{115,116}

Two epidemiological studies of associations between cosmetic use and breast cancer in the general population have been published. In a population-based case-control study of 813 case subjects and 793 controls, self-reported underarm antiperspirant/deodorant use was not associated with an increased risk of breast cancer.¹¹⁷ This study is limited by the potential

for exposure misclassification inasmuch as paraben exposures were not actually measured and the study was unable to take into account other potential sources of parabens in cases or controls.

In a retrospective study of 437 women diagnosed with breast cancer, frequency of use and early onset use of deodorants/antiperspirants were associated with an earlier age of breast cancer diagnosis.¹¹⁸ This study lacked age adjustment and controls. It was also undertaken when deodorant use and breast cancer rates were both increasing, but the two could be totally unrelated.

Whether or not parabens have any relationship to breast cancer risk remains unresolved. But human exposures to parabens from various sources are nearly ubiquitous.¹¹⁹ This is, therefore, an important public health concern and highlights the need for controlled and detailed evaluation of breast cancer risk from personal care products, taking into account product ingredients, effect of formulations, and total quantities applied, especially in potentially highly sensitive subgroups such as babies and children.¹²⁰

Cadmium

Human exposures to cadmium come from breathing cigarette smoke and polluted air from fossil fuel and municipal waste combustion. Workers can be exposed by breathing air from the smelting or refining of metals or in factories manufacturing batteries, coatings, or plastics. Cadmium is also in pigments and plastics in many consumer products, including children's toys. Food grown in contaminated soil can contain cadmium. Exposures are widespread in the general population.¹²¹ Cadmium is toxic to the lungs, kidneys, testes, and placenta.¹²² It causes cancer in multiple organs in experimental animal studies, probably through multiple mechanisms including genotoxicity, altered gene expression, disruption of gene repair, and production of reactive oxygen species.¹²³ It is also estrogenic. The EPA classifies cadmium as a probable human carcinogen.

- Prenatal exposure to low levels of cadmium alters mammary development in mice and rats, mimicking the effects of estrogen. *In utero* exposure to cadmium at levels similar to those in the humans cause increased numbers of terminal end buds and reduced alveolar buds in the mammary glands in adulthood.¹²⁴
- A case-control study of urinary cadmium levels in 246 women with breast cancer in Wisconsin found a two-fold higher risk in women with the highest levels of urinary cadmium compared to the lowest, after adjustment for other risk factors, including smoking.¹²⁵

- A case-control study of 153 women with breast cancer and 431 controls found a six-fold higher risk in women with the highest levels of urinary cadmium compared to those with the lowest levels.¹²⁶ Cadmium levels in the most highly exposed women were higher than in the Wisconsin women in the previous study.
- A case-control study of 100 women with breast cancer in New York and 98 controls found that women in the highest quartile of urinary cadmium had more than twice the risk (OR=2.69) compared to women in the lowest quartile.¹²⁷ The same authors found a similar increased risk in 92 women with breast cancer and 2,884 without from the 1999-2008 NHANES cohort.

Atrazine

Atrazine is a widely-used agricultural herbicide, and it is a common surface and groundwater contaminant to which many people are exposed.^{128,129}

- In some rodent studies, atrazine and its metabolites cause abnormal and delayed mammary gland development, resulting in less ductal branching and fewer but more persistent TEBs¹³⁰ while others find no long term effects on mammary gland development.¹³¹ However, since different rat strains were used in these conflicting studies and experimental procedures differed as well (researchers discarded some mammary gland specimens that did not contain the entire ductal network in the study finding no effect), it's difficult to draw firm conclusions. Atrazine can also alter puberty timing in various rodent strains, although the doses at which this occurs are unlikely to be encountered by people.¹³²
- Lifetime dietary exposure to atrazine in Sprague-Dawley rats causes increases in mammary gland cancer. However, there is considerable debate about whether atrazine should be considered a human carcinogen. In these rats, atrazine suppresses luteinizing hormone secretion resulting in a state of persistent estrus. It is hypothesized that this results in prolonged exposure to elevated levels of estrogen and prolactin, which may foster the development of mammary gland cancer in older animals.¹³³ If true, this mechanism of action may not be relevant to humans.¹³⁴ However, since atrazine can also alter puberty timing in various rodent strains and alter mammary gland development and milk production, other mechanisms that are relevant to humans may influence breast cancer risk. This debate remains unresolved.

Perfluorinated compounds (PFCs)

Perfluorinated compounds are a family of chemicals long used as surfactants, to impart stain resistance and as water repellants on materials and fabrics, and for non-stick properties

on cooking utensils. They are environmentally persistent and many are bioaccumulative. Human exposures are widespread, mostly from diet and contaminated drinking water and dust.¹³⁵ Perfluorooctanoic acid (PFOA) is a breakdown product of members of this family of chemicals containing eight carbon atoms in the molecular backbone. Studies in mice show altered mammary gland development after gestational exposure to PFOA at levels similar to some more highly exposed people.^{136,137}

Few human studies have attempted to examine the relationship between PFCs and breast cancer risk. A case-control study of Inuit women in Greenland found significantly higher levels of PFCs in the serum of cases compared to controls.¹³⁸ Women with breast cancer were more likely to be pre-menopausal than controls. The women with breast cancer also had higher levels of PCBs. This study is limited by incomplete pregnancy information for a number of participants.

A study of cancer incidence in an area contaminated with PFCs from a nearby DupontTeflon manufacturing plant used drinking water levels of PFOA to estimate serum levels among residents.¹³⁹ Investigators found increases in testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma—but not breast cancer—associated with higher estimated serum levels of PFOA.

Dioxins

Dioxins are a family of chlorine-containing chemicals formed by waste incineration, metal smelting, coal fired boilers and cement kilns burning hazardous waste.¹⁴⁰ Burning waste containing polyvinylchloride (PVC), which contains large amounts of chlorine, can produce significant amounts of various dioxins, depending on temperature and operating conditions of the incinerator. Back yard burn barrels are notorious sources of dioxin emissions.

The toxicity of dioxins varies with number of chlorine atoms attached to the basic molecular structure. In general, dioxins are persistent and bioaccumulative. Half-lives of dioxins in humans range from seven to eleven years.¹⁴¹ Human exposures to dioxin are largely from consuming contaminated food. Fortunately, dioxin levels in humans are decreasing as a result of more stringent controls on environmental releases.

The toxicity of dioxin is mediated through attachment to the aryl hydrocarbon receptor (AhR), a nuclear receptor involved in metabolism of environmental chemicals, among other functions. Activated AhR also interacts with the estrogen receptor, resulting in what sometimes appears to be an anti-estrogenic effect.¹⁴²

The International Agency for Research on Cancer (IARC) and the National Toxicology Program list the most potent dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), as a known

human carcinogen. This is based on occupational studies showing increased cancer mortality in more highly exposed individuals. With regard to breast cancer, dioxins do not induce mammary tumors in adult rats, but rats with pre-natal exposure to TCDD undergo altered mammary gland development and are more susceptible to DMBA-induced mammary tumors.¹⁴³ This does not, however, occur in mice, in which prenatal exposure to TCDD delays and reduces DMBA-induced mammary tumors.¹⁴⁴

A 1991 study of workers exposed to dioxin in a German herbicide-production facility reported excess deaths from breast cancer among women.¹⁴⁵ An industrial explosion in Seveso, Italy in 1976 exposed a large population of people to substantial amounts of TCDD. Blood levels of TCDD in residents were measured and ongoing studies continue to look for evidence of excess cancer and other health outcomes. After twenty years of follow up, women in the zone most highly contaminated with TCDD experienced a significant 2.5-fold increased risk of breast cancer.¹⁴⁶ Women who were young girls at the time of the incident are just reaching the age when breast cancer is more likely, and future studies are forthcoming.

Additional chemical agents

Alcohol and other solvents

Many studies conclude that alcohol ingestion is a risk factor for breast cancer, and the effects of alcohol may begin early in life. In laboratory animals, pre-pubertal exposure to moderate levels of alcohol alters development of the mammary gland, resulting in increased numbers of TEBs and fewer more mature structures after puberty.¹⁴⁷

Beginning in the 1980s, case-control studies reported 2-2.5 fold increased risk of breast cancer in women who ingested any alcohol compared to women who did not drink.^{148,149,150} Since then, more than 100 epidemiologic studies have been conducted, confirming an increased risk, and the IARC has concluded that alcohol consumption is causally related to breast cancer.¹⁵¹ A recent review of studies examining risks associated with low levels of alcohol consumption finds about a four percent increased risk of breast cancer at intakes of up to one alcoholic drink/day and 40-50 percent increased risk associated with three or more drinks/day.¹⁵² It should be noted, however, that the slight increased risk associated with one alcoholic drink daily represents a very small increased individual risk and should be considered alongside the cardiovascular benefits associated with a similar level of alcohol ingestion. Coronary artery disease is a more common cause of death in post-menopausal women than breast cancer.¹⁵³

The mechanisms by which alcohol may increase breast cancer risk are not well understood. They may include increased estrogen levels associated with alcohol ingestion (unlikely in

post-menopausal women), exposure to toxic metabolites, and increased oxidative stress that can damage DNA.¹⁵⁴

Although a number of animal studies show increases in mammary gland cancer with exposures to other organic solvents, studies in humans are few and generally inadequate. Exposure assessments are often poor, follow up periods too short for a disease with long latency like breast cancer, and most occupational studies have historically focused on men. An exception is the previously mentioned study of a breast cancer cluster at Canadian General Electric implicating methylene chloride and trichloroethylene.

One population-based study in which the investigators undertook extensive efforts to estimate exposure levels found a 50-100 percent increased risk of breast cancer in women in a community exposed to higher amounts of perchlorethylene that had leached into their drinking water from the polyvinylchloride pipes in the water distribution system.^{155,156}

A retrospective cohort study of over 270,000 women in the military found a 48 percent increased risk of breast cancer in women less than 35 years of age with moderate to high exposure potential to one or more volatile organic compounds, many of which are solvents.¹⁵⁷ Several other studies also show an increased risk of breast cancer with occupational exposure to solvents.^{158,159,160,161}

A recently identified cluster of breast cancer in men who lived for varying periods of time at the U.S. Marine base at Camp Lejeune in North Carolina where drinking water was contaminated with trichloroethylene and other organic solvents is actively being investigated by the Centers for Disease Control and Prevention.¹⁶²

Polycyclic aromatic hydrocarbons (PAHs)

Evaluation of the cancer causing potential of PAHs in humans is complicated by the hundreds of forms of PAHs with differing compositions and properties. The IARC reviewed sixty PAHs, with separate classifications for individual compounds.¹⁶³ They concluded that benzo(a)pyrene (BaP) was carcinogenic to humans (Group 1) “based on sufficient evidence in animals and strong evidence that the mechanisms of carcinogenesis in animals also operate in exposed human beings.”¹⁶⁴ Several other PAHs were classified as probably carcinogenic in humans.

The results of studies of the effects of estimated dietary PAHs on breast cancer risk in people are inconsistent. A few studies have attempted to assess risks associated with certain periods of exposure. A case-control study in New York examined exposure to traffic emissions at specific times on the basis of residence.¹⁶⁵ Higher exposure at the time of menarche was associated with increased risk for premenopausal breast cancer (OR = 2.05; 95% CI 0.92–

4.54) Higher exposures at the time a woman had her first birth were associated with a significantly increased risk for postmenopausal breast cancer (OR = 2.57, 95% CI, 1.16–5.69)

Studies looking at biomarkers of PAH exposures after diagnosis of breast cancer are also inconsistent. In the population-based, case-control Long Island Breast Cancer Study, the presence of PAH-DNA adducts, which form after exposure to PAHs and are measured in white blood cells, were associated with a 29 to 35 percent increase in the risk of breast cancer.¹⁶⁶ In contrast, results from the case-control Shanghai Women's Health Study found no association between PAH metabolites and oxidative stress markers and breast cancer.¹⁶⁷

Some of the inconsistencies in findings in different studies may be due to genetic differences in DNA-repair mechanisms. For example, in the Long Island breast cancer study, variations in genetic profiles associated with DNA repair influenced the breast cancer risk associated with PAH exposures.¹⁶⁸

The IOM committee report concluded that epidemiologic studies of PAHs provide modest support for their ability to cause human breast cancer (See Box 5.2).

Ethylene oxide

Ethylene oxide is a highly reactive gas used mainly as a chemical intermediate in the manufacture of textiles, detergents, polyurethane foam, antifreeze, solvents, pharmaceuticals, adhesives, and other products. Smaller amounts are used as a fumigant, a sterilant for food (spices) and cosmetics, and in hospital sterilization of surgical equipment and plastic devices that cannot be sterilized by steam.¹⁶⁹

Exposure to ethylene oxide occurs mainly in the workplace, including hospitals. It is classified as a human carcinogen by both IARC and NTP on the basis of evidence from epidemiologic and animal studies. Some studies find an increased risk of breast cancer in women exposed to the sterilant ethylene oxide in health care facilities or manufacturing plants in which the chemical is used.^{170,171} The IOM committee report concluded that ethylene oxide is plausibly related to breast cancer risk after adult exposures.

BOX 5.2: The Institute of Medicine report

In their 2012 report “Breast Cancer and the Environment: A life course approach,” a committee convened by the Institute of Medicine reviewed the evidence linking select environmental variables to breast cancer incidence.¹⁷² It was not a comprehensive review. The committee selected a limited set of factors from an extensive list in order to illustrate a variety of environmental exposures, and to emphasize the need for new approaches to research into environmental risks for breast cancer. The committee did not review dietary variables.

For this review, the chemicals the committee selected included:

- Exogenous hormones: hormone replacement therapy (HRT), oral contraceptives (OCs)
- Consumer products and constituents: alkylphenols, bisphenol A, nail products, hair dyes, parabens, perfluorinated compounds, phthalates, polybrominated diphenyl ethers (a family of flame retardants)
- Industrial chemicals: benzene, 1,3 butadiene, PCBs, ethylene oxide, vinyl chloride
- Pesticides: DDT/DDE, aldrin, dieldrin, atrazine
- PAHs
- Dioxins
- Metals: Cadmium, arsenic, aluminum, lead, iron, mercury

The committee concluded that:

- The clearest evidence from epidemiologic studies of increased risk of breast cancer were: combination (estrogen-progestin) hormone therapy products, current use of oral contraceptives, alcohol consumption, and exposure to ionizing radiation.
- Some but not all reviews find active tobacco smoking causally related to increased risk of breast cancer.
- The evidence linking passive smoking, shift work involving night work, benzene, 1,3-butadiene, and ethylene oxide to increased risk is less strong but suggestive. For bisphenol A, zearalenone*, vinyl chloride, and alkylphenols†, human epidemiologic evidence regarding breast cancer is not available or inconclusive, but laboratory studies provide a biologic basis for concern that they may increase risk.

* Zearalenone is a potent estrogenic compound produced by some species of fungi. It can contaminate some kinds of food, particularly corn.

† Alkylphenols are chemicals used in the production of detergents and other cleaning products, and as antioxidants in products made from plastics and rubber. They are also found in personal care products, especially hair products, and as an active component in many spermicides. Some alkylphenols or their breakdown products are estrogenic.

- Non-ionizing radiation and personal use of hair dyes, have not been associated with breast cancer risk in multiple, well-designed human studies.
- For several other factors, evidence was too limited or inconsistent to reach a conclusion (e.g., nail products, phthalates).
- For most of the factors examined, information on the potential for exposure at different life stages to affect risk is limited or nonexistent.
- There is a need for future research “to better reflect the growing understanding of a life course perspective whereby the potential for influencing breast cancer risk may depend exquisitely on the timing of exposure, and an appreciation of the potential for different factors to play a role in specific, etiologically distinct varieties of breast cancer based on histologic or molecular subtype.”

Among their high priority research recommendations, the committee called for more systematic and urgent investigation of:

- Chemicals with endocrine activity,
- Interactions between chemicals, such as BPA, polybrominated diphenyl ethers (PBDEs), zearalenone, and certain dioxins and dioxin-like compounds,
- The importance of timing of exposure, diet, and other factors that may influence the relationship of these types of compounds to breast cancer risk.

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