

State of the Evidence

The Connection Between Breast Cancer and the Environment

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A substantial body of scientific evidence indicates that exposures to common chemicals and radiation, alone and in combination, are contributing to the increase in breast cancer incidence observed over the past several decades. Key recurring themes in the growing scientific literature on breast cancer and environmental risk factors are: (a) the importance of understanding the effects of mixtures and interactions between various chemicals, radiation and other risk factors for the disease; and (b) the increasing evidence that timing of exposures matters, with exposures during early periods of development being particularly critical to later risk of developing breast cancer. A review of the scientific literature shows several classes of environmental factors have been implicated in an increased risk for breast cancer, including hormones and endocrine-disrupting compounds, organic chemicals and by-products of industrial and vehicular combustion, and both ionizing and non-ionizing radiation. *Key words:* breast cancer; endocrine disruptors; radiation.

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Increasingly sophisticated and compelling data link radiation and various chemicals in our environment to the current high rates of breast cancer incidence. We acknowledge the importance of many widely understood risk factors for breast cancer, including primary genetic mutations,¹ reproductive history,² and lifestyle factors such as weight gain,³ alcohol consumption^{4,5} and lack of physical exercise.⁶ Yet we begin with an understanding that these factors alone still do not address a considerable portion of the risk for the disease.⁷ A substantial body of scientific evidence indicates that exposures to common chemicals and radia-

tion, alone and in combination, may contribute to the unacceptably high incidence of this disease.

In this review, we focus on studies on environmental agents such as pesticides, dioxin, secondhand tobacco smoke, plasticizers and other chemicals, as well as many forms of radiation.

We do not discuss the often complicated and inconclusive literature examining possible relationships between diet, stress or obesity and risk for breast cancer.³

In a companion piece in this issue, the authors of this article add to this review by outlining how the growing scientific data connecting certain environmental chemicals and radiation to breast cancer incidence can inform and direct new research as well as federal and state public policy to reduce environmental exposures.

BACKGROUND

Breast Cancer Statistics

Breast cancer now affects more women in the world than any other type of cancer except skin cancer. In the United States, a woman's lifetime risk of breast cancer increased steadily and dramatically from the 1930s, when the first reliable cancer incidence records (starting in the state of Connecticut) were established, through the end of the 20th century.^{8,9} Between 1973 and 1998, breast cancer incidence in the United States increased by more than 40%.¹⁰ Today, a woman's lifetime risk of breast cancer is one in eight.

The most recent incidence data (for the years 2003 and 2004)¹⁰⁻¹² indicate a significant decline in breast cancer incidence for women in the U.S., although this effect may be relevant only for women over the age of 50 with a particular sub-type (estrogen-receptor positive or ER+) of the disease.¹³⁻¹⁵ The most widely discussed explanation for this decrease is the sharp drop in use of post-menopausal hormone replacement therapy (HRT) over the past few years. The decline in use of HRT was especially notable following the 2002 publication of results from the Women's Health Initiative linking combined estro-

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gen plus progestins HRT with increased risk for breast cancer.^{13,16} According to Colditz, this rapid change in postmenopausal ER+ incidence rates in close temporal proximity to a decrease in HRT use suggests a promoter effect of estrogens plus progestins for breast cancer development.¹⁷

The incidence of breast cancer varies considerably by a number of factors, including age and ethnicity. In the U.S. between 2000 and 2004, white¹⁸ women had the highest overall annual incidence rate for the disease (132.5 cases per 100,000 women), followed by African American (118.3 per 100,000), Hispanic (89.3 per 100,000), Asian American/Pacific Islander (89.0 per 100,000) and American Indian/Alaska Native (69.8 per 100,000) women.¹⁰ The great majority of women diagnosed with breast cancer are 45 years of age or older, and a higher rate of the disease is found for white women as compared to African American women for all ages over 45. Nevertheless, in those age 35 and younger, there is a higher incidence rate for African American than white women.¹⁹ Most importantly, younger women in general, and younger African American women in particular, present with forms of the disease that are more aggressive and more difficult to treat effectively.^{20,21}

Looking at national mortality data and aggregating across all possibly affected organs, cancer is the leading cause of death for U.S. women between the ages of 40 and 79, and the second most prevalent cause of death, after heart disease, for all other ages. Cancer of the breast results in the highest mortality rates of any cancer in women 20–59 years of age. Although rates of mortality from breast cancer remain high for older women, lung cancer is responsible for more deaths among the elderly.^{11,22}

Globally, more than 1.15 million women were diagnosed with breast cancer in 2002.^{23,24} The highest rates are found in the industrialized nations of North America and western Europe, while lower rates are generally found in western Asia, southern Africa and South America, although even in these areas cancer of the breast is the most commonly diagnosed cancer in women.²³ In northern Africa, as in many countries that are either developing or in transition, breast cancer rates are escalating sharply.^{23,25,26} While some of the changes in rates may be associated with improved ability to detect the disease along with changes in lifestyle and reproductive histories, migration studies suggest that much of the variability in international incidence rates might be environmentally related.

Migration Studies

Women who move from countries with low breast cancer rates to nations with higher rates soon acquire the higher risk of their new country. For example, women who immigrate to the United States from Asian

countries, where the rates are four to seven times lower, experience an 80% increase in risk after living in the United States a decade or more.^{27,28} A generation later, the risk for their daughters approaches that of U.S.-born women. Hispanic women born in the U.S. have a significantly higher rate of breast cancer than do immigrant Hispanic women.²⁹ The longer immigrant Hispanic women spend in the U.S., the greater their risk for breast cancer. This is especially true for women who immigrated before the age of 20.

Similarly, a Swedish study of patients with various cancers found that age at immigration determined whether the individual acquired the cancer risk of the country of origin or the country of destination.³⁰ Hemminki and Li concluded that, “Birth in Sweden sets the Swedish pattern for cancer incidence, irrespective of the nationality of descent, while entering Sweden in the 20s is already too late to influence the environmentally imprinted program for the cancer destiny.”

Immigration to industrialized countries may alter many factors. The breast cancer risk of immigrants—and that of their daughters—may increase if they adopt a Western lifestyle. If diet plays a role, the increased risk could result from nutritional content, contaminants or food additives, or a combination of these factors. Emigration may also affect reproductive behavior, such as the use of oral contraceptives²⁷ or when and if a woman decides to have children. Moving to a more industrialized society may also increase exposures to environmental pollutants.³¹

A growing body of evidence from both human and animal models (see *Timing of Exposures*, below) indicates that exposure of fetuses, young children and adolescents to radiation and environmental chemicals puts them at considerably higher risk for breast cancer.³² These data are consistent with the role of environmental exposures, especially at young ages, in affecting the later incidence of breast cancer in women who have immigrated to relatively industrialized areas from regions of the world with lower risks of breast cancer.

Gene-Environment Interactions

Another indicator that environmental changes over the past several decades may be influencing breast cancer risk comes from studies looking at incidence rates in women with primary genetic mutations related to the disease. Inherited mutations of the two “breast cancer genes,” *BRCA1* and *BRCA2*, have received much attention recently, although they may account for a relatively small fraction—no more than 10%—of the current breast cancer diagnoses.³³ These mutations do greatly increase the risk for breast cancer, especially among members of families with a history of either breast or ovarian cancer. However, having a mutation in either of these genes does not necessarily mean that a woman will develop the disease.

BREAST CANCER RATES ARE FALLING?

Recent data indicate a significant decrease in breast cancer incidence in the United States. These data are the first indications in decades that the sum of factors leading to the development of breast cancer may be receding. Most notably, several reports in the recent scientific literature have associated these decreases in (ER+, post-menopausal) breast cancer rates with very recent decreases in use of post-menopausal hormone replacement therapy (HRT).

There could be other factors contributing to this decline. It has been three decades since many pesticides, including DDT, have been banned. Although we all carry remnants of DDT's earlier large-scale usage, concentrated exposures during critical periods of breast development are much lower than they were for young girls several decades ago.

Similarly, federal and state regulations have succeeded in removing from common use several other chemicals that have been implicated in the rising risk for breast cancer. For example, our air is generally cleaner than it was 35 years ago, reducing exposure to polycyclic aromatic hydrocarbons (PAHs) and other air pollutants linked to breast cancer. And smoking restrictions in workplaces and public spaces have greatly reduced exposures to secondhand smoke, a factor that is especially important for young children and adolescents.

Short term patterns of disease incidence, including breast cancer may not reflect long-term trends. Still, declines in breast cancer rates provide real promise for the future that by decreasing exposures to exogenous estrogens, estrogen mimics, endocrine disruptors and other carcinogens, we may continue to lower the levels of breast cancer and eventually prevent the disease in the future.

Women with an inherited mutation on the *BRCA1* or *BRCA2* gene have a 60–82% probability of being diagnosed with breast cancer in their lifetimes.³⁴ This suggests that the likelihood of developing breast cancer is influenced by something beyond the identified mutations or the lifestyle and environmental factors that are often shared by members of the same family. In other words, differences in personal and environmental exposures probably contribute significantly to whether the *BRCA1* or *BRCA2* mutations are associated with a diagnosis of breast cancer.

In studies of both U.S.^{34,35} and European³⁶ women with *BRCA1* or *BRCA2* mutations, those who demonstrated higher incidence of the disease were born in recent decades that parallel increasing exposures to a wide variety of synthetic chemicals implicated in increased risk for the disease. For example, female *BRCA1* carriers born after 1940 have nearly twice as much breast cancer by ages 40 and 50 as those born earlier.³⁴ These younger women were more likely than their older relatives to have been exposed to radiation from military, medical or accidental sources, or to potentially toxic chemicals during the sensitive periods of their early development.

Other studies have explored the relative contributions of genetic and environmental factors by examining likelihood of disease in twins. In the largest study of twins ever conducted, researchers found that, among twins in which at least one woman developed breast cancer, environmental exposures unique to that woman made the most significant contribution to the development of the cancer.³⁷ Inherited genes were found to contribute 27%, shared environmental factors 6%, and non-shared environmental factors 67% of the risk. These data indicate that most breast cancer is not inherited. A recent re-

analysis of this study concluded that “genetic susceptibility makes only a small to moderate contribution” to the incidence of breast cancer.^{38,39}

Recent studies have identified several genes that may increase breast cancer risk.^{40–43} How these genetic profiles might interact with one another, or with reproductive, lifestyle, or environmental factors in increasing breast cancer risk remains to be examined.

Chemicals in our Environment and in our Bodies

As suggested above, the rising incidence of breast cancer in the decades following World War II paralleled the proliferation of synthetic chemicals. An estimated 80,000 synthetic chemicals are used today in the United States, and another 1,000 or more are added each year.⁵⁸ Yet complete toxicological screening data are available for just 7% of these chemicals and more than 90% have never been tested for their effects on human health.⁵⁹

A recent survey indicated that 216 chemicals and radiation sources have been registered by international and national regulatory agencies as being experimentally implicated in breast cancer causation.^{60,61} Many of the chemicals persist in the environment⁶² and accumulate in body fat and may remain in breast tissue for decades.^{63,64} (See Appendix 1 for a listing of chemicals that have been registered by the International Agency for Research on Cancer [IARC] as carcinogens, and that have also received ratings by regulatory agencies regarding induction of human breast and animal mammary tumors.)

Studies by the U.S. Centers for Disease Control and Prevention of chemical body burdens show that all Americans carry many contaminants in their bodies, and that women have higher levels of many of these

BREAST CANCER INCIDENCE AND MORTALITY BY RACE AND ETHNICITY

Breast cancer incidence and mortality rates vary widely among racial/ethnic groups, among various age groups and among the populations of counties, states and countries. Globally, incidence is highest among white women of European descent who live in industrialized countries. Still, a global view is like an aerial photograph: it doesn't show the details of what's happening on the ground—in communities and in individuals.

Although diversity is increasing in the U.S., medical and scientific research on diverse populations has not kept pace. Much of current breast cancer diagnosis and treatment is based on research in white women. Breast cancer among women of color is only beginning to be addressed. Even so, evidence shows genetic variations affect susceptibility to environmental exposures as well as the characteristics of the tumors themselves. It is also clear that breast cancer is more aggressive in some racial/ethnic groups than in others.

Incidence

White (non-Hispanic) women of all ages have the highest incidence of breast cancer of any racial/ethnic group in the United States. American Indian/Alaska Natives have the lowest incidence of the disease.⁴⁴ Latinas have a much lower incidence of breast cancer than either black or white women, but the figure is rising.

Black women younger than age 35 have a higher incidence of breast cancer than their white counterparts, and a less favorable prognosis. They have more aggressive tumors: typically estrogen-receptor negative, progesterone-receptor negative, HER2 negative and basal-type tumors, sometimes referred to as "triple-negative" tumors. Triple-negative tumors do not respond to hormonal therapies such as tamoxifen.^{45,46} In addition, young black women present with more advanced breast cancer at diagnosis, including larger tumors and more lymph node involvement.⁴⁷

Throughout the 1990s, the incidence of inflammatory breast cancer (IBC), a rare type that primarily affects premenopausal women, increased in both black women and white women.⁴⁸ However, the incidence of IBC is higher among black women. Because IBC does not cause a lump in the breast, it may be misdiagnosed as an infection, leading to delays in treatment.

Some findings suggest that breast cancer risk factors are different for black women and white women. Early age at first birth and having four or more children before age 45 appear to increase the risk of breast cancer in black women, while in white women early childbearing reduces breast cancer risk.⁴⁹ Use of oral contraceptives may increase the risk of breast cancer in black women, apparently by raising levels of insulin-like growth factor-1 (IGF-1), which is associated with increased risk of breast cancer. On the other hand, oral contraceptive use suppresses levels of IGF-1 in white women.⁵⁰

Mortality

Black women have the highest breast cancer mortality rate of any racial/ethnic group. Asian Americans, particularly Japanese Americans and Chinese Americans, have the best survival rates.¹⁹ The reasons for these disparities are not

chemicals than do men.⁵¹ Some of these contaminants, including chemicals used in common fuels, solvents and industrial processes, have been linked to mammary tumors in animals.^{59,65}

Many of these chemicals have recently been shown to be detectable in young girls (age 6–8 years) living in New York, Ohio and California.⁶⁶ Some of these chemicals are found in maternal blood, placental tissue and breast milk samples from pregnant women and mothers who have recently given birth, indicating that maternal burdens of environmental contaminants are being passed on to their young during pregnancy and breastfeeding.^{67–70} This is of great concern, given increasing evidence that chemical exposures during prenatal through adolescent periods have profound lifelong impacts on breast tissue development and possible susceptibility to cancer later in life.

MAIN THEMES: MIXTURES AND TIMING OF EXPOSURES MATTER

Two themes recur in the complex and sometimes controversial evidence related to environmental risks and breast cancer. The first theme is that mixtures matter. It is extremely difficult to study and understand chemical interactions, yet growing evidence supports the need for an examination of the multiple factors that may increase risk for breast cancer.⁷¹ The second recurring theme is that timing of exposure matters. Growing scientific evidence from human epidemiological studies and animal-based toxicological studies indicates that exposures to environmental chemicals and radiation during early development may predispose a woman to higher risk of breast cancer.

clearly understood. However, socioeconomic factors undoubtedly play a role in both environmental exposures and access to care. According to CDC scientists, when compared to whites or Mexican Americans, blacks have higher blood and tissue levels of some chemicals, such as polychlorinated biphenyls (PCBs), mercury, lead, PAHs, dioxin and phthalates. Mexican Americans have higher levels of the pesticides lindane, 2,4,5-trichlorophenol, and DDT and its metabolite DDE.⁵¹ Biomonitoring can provide important information about differences in exposures that must be considered in investigating the causes of breast cancer.

Breast cancer is the leading cause of cancer death in Latinas in the U.S. Like young black women, Latinas are also disproportionately affected by aggressive triple-negative tumors.⁵² Environmental exposures may be contributing to the rising rates, particularly among farm workers.⁵³ Research also shows that hormone therapy may pose a greater risk of breast cancer in post-menopausal Latinas than in their white counterparts.⁵⁴

American Indian/Alaska Native (AI/AN) women have the lowest incidence of breast cancer and one of the lowest mortality rates. However, the American Cancer Society urges caution in interpreting these statistics, stating: "Cancer incidence rates among the American Indian population have been monitored more systematically in the Southwest than in other geographic regions and may not reflect the cancer experience of American Indians or Alaska Natives residing elsewhere."¹⁹ The National Cancer Institute's SEER (Surveillance Epidemiology and End Results) data for AI/AN populations predominantly reflect the cancer rates for those living on reservations covered by the New Mexico registry and in urban areas in California. Therefore, it is possible that many cases of breast cancer may go unreported, particularly among women living in rural reservations with limited access to health care.

Research Implications

Research on breast cancer in racial/ethnic populations needs to recognize that genetic, cultural and historical diversity exists within those populations. For example, African Americans are heterogeneous in terms of the region of Africa from which their ancestors came.⁵⁵ Hispanic/Latino Americans include people from Cuba, Mexico, Puerto Rico, Central and South America, Dominican Republic and other countries, who have various racial and ethnic backgrounds. Asian/Pacific Islander Americans include many nationalities/ethnic groups—Chinese, Filipinos, Koreans, Hawaiians, Indians, Japanese, Samoans, Vietnamese and others. The AI/AN population represents more than 500 diverse tribes with different cultures, socio-demographic factors and languages.⁵⁶

Reporting cancer statistics according to broad racial and ethnic groupings may mask wide variations for specific groups within those broad categories. For example, a study of Asian American women in Los Angeles found that breast cancer risk among women of Japanese and Filipino ancestry is twice that of Chinese and Korean women. Asian women, who have relatively low breast cancer rates in their native countries, experience increasing breast cancer incidence after immigrating to the U.S.⁵⁷

A more detailed understanding of breast cancer among women of color is urgently needed. Research needs to move beyond examining patterns of mammography screening among various ethnic groups. Future research should include occupational studies and biomonitoring to determine exposures, as well as analyses to determine tumor characteristics within various racial/ethnic groups.

Mixtures Matter

It is very difficult to design and conduct reliable, long-term studies examining the possible effect of individual chemicals on risk for a disease as complex as breast cancer. Women are not exposed to chemicals in isolation, the time between exposures and development of the disease may be several decades, and women cannot know most of the chemicals to which they have been exposed. Numerous animal studies indicate that the kinds of mixtures to which an animal is exposed may have additive or synergistic effects.⁷² However only a few combinations and doses of chemicals have been tested. Koppe and colleagues have calculated that it would require 166 million experiments to test all combinations of just three of the 1,000 most commonly used synthetic chemicals (of about 80,000) currently in

use.⁷³ While only a few of those studies have been conducted, several of them indicate either additive or synergistic effects of mixtures of low levels of chemicals in a number of systems that are relevant to exploring risk for breast cancer.

Of course, each chemical in isolation may have different effects depending on the concentration and timing of exposures. There are several examples in the recent scientific literature demonstrating that mixtures of environmental chemicals, chemicals and radiation, or complex combinations of chemicals and particular genetic or hormonal profiles may alter biological processes and possibly lead to increases in breast cancer risk. In a variety of studies, the combination of two weakly estrogenic pesticides—dieldrin and toxophene—was shown to have either additive⁷⁴ or synergistic⁷⁵ effects, depending on the doses used and the

particular conditions of the experiments. Similarly, combinations of very low doses of common chemical surfactants (used to solubilize or disperse other chemicals) and herbicides led to highly synergistic effects in a natural wildlife fish model that, like human breast tissue, is sensitive to estradiol and related estrogenic compounds⁷⁶ Payne et al. used the yeast estrogen screen (YES), an in vitro assay of estrogen receptor activation, to examine the combined effects of mixtures of a pesticide residue (o,p'-DDT), a plant estrogen (genestein, found in soy), and two alkylphenol surfactants (sudsing agents and chemical dispersers; 4-n-octylphenol and 4-nonylphenol). Clear additive effects of the four chemicals were observed.⁷⁷

Rajakpase et al. looked at the combined effects of 11 different environmental contaminants—all added at levels so low that they did not have any effects in isolation—and found the various chemicals had additive effects with each other and also with naturally occurring estradiol.⁷⁸ Similarly, at levels found in the environment, the ubiquitous plasticizer bisphenol A significantly increased the effects of estradiol.⁷⁹ These results show that even at low concentrations, environmental chemicals may exacerbate some of the biological effects of natural estrogens.

Together, these toxicology studies suggest that many of the chemicals of concern may mimic or functionally increase the action of natural estrogens. Excess exposure to estradiol and its related compounds is believed to be the pathway which explains how many commonly discussed risk factors such as reproductive history (age at first menstruation, number of children, age at menopause, contraceptive and hormone replacement history, etc.), diet, and alcohol consumption effect breast cancer risk.⁸⁰

In a study of mammary tissue development, rats with prenatal exposures to mixtures of chemicals commonly found in the environment had higher levels of mammary tissue abnormalities when exposed to dietary estrogens after birth.⁸¹ These profound tissue abnormalities have been associated with mammary tumors.⁸² Similarly, young rats exposed to a low dose of radiation showed earlier appearance and increased frequency of *H-ras* mutated mammary tumors after subsequent exposure to a known chemical carcinogen.⁸²

Recent large clinical studies of women with breast cancer have explored the effects of exposures to environmental chemicals and radiation in combination with other factors. The data from these studies illustrate how complex the interactions among breast cancer risk factors may be. The data also help clarify why large epidemiological studies examining the effects of different chemicals on breast cancer risk in women may have contradictory results.

For example, in a study examining the possible link between organochlorine pesticide residues and breast cancer among African American and white women in

North Carolina, higher blood (plasma) levels of the chemicals did not correspond to a diagnosis of breast cancer.⁸³ But the data did suggest that race/ethnicity, body mass, reproductive history and social factors might make some women more susceptible to the carcinogenic effects of the organochlorine pesticides.

A number of other studies suggest that specific combinations of genes may make some women more vulnerable to certain environmental carcinogens.^{83–85} These studies suggest that for many women, genetic and other commonly discussed factors may interact with environmental carcinogens in causing a large number of breast cancer cases. These differences do not only occur in primary breast cancer genes like *BRCA1* or *BRCA2*. That is, they are not indicated in heritable transmission of the disorder from generation to generation in the way that the *BRCA* gene mutations are. Nevertheless, these mutations may make a woman more susceptible to the effects of environmental carcinogens.

Rather than looking for single, direct causes underlying the disease, we will be better served to recognize the multiple and interacting factors that may influence risk. It is time to look beyond simple linear cause-effect relationships between risk factors and breast cancer, or assign proportions of risk that may be attributed to various factors. Instead, we need to begin to think of breast cancer causation as a complex web of often-interconnected factors, each exerting both direct and interactive effects on cellular and extra-cellular processes in mammary tissue.

Timing of Exposures Matters

Two decades of research on laboratory animals, wildlife, and isolated cell systems have shown the inadequacy of the long-held belief that “the dose makes the poison.” In fact, lower exposures to chemicals may sometimes have more profound effects than higher ones, making research into environmental risks and disease even more challenging.⁸⁶ When examining the effects of lifestyle factors, environmental chemicals, and radiation on future breast (mammary) cancer induction, timing, duration, and pattern of exposure are at least as important as the dose.⁸⁷ Mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation during early stages of development, from the prenatal period through puberty and adolescence, and on until the first full-term pregnancy.⁸⁸

Prenatal Exposures. It is exceedingly difficult to separate fetal exposures to environmental chemicals and radiation from sustained exposures over a lifetime. Substantial barriers exist to recalling and documenting mothers' exposures 30 to 60 years a woman's birth.

An estimated 5–10 million American women took diethylstilbestrol (DES) between 1938 and 1971,⁸⁹

resulting in structural abnormalities in their daughters' reproductive tracts leading to later infertility and increased vaginal and cervical cancer rates.⁹⁰ Evidence over the past decades shows an association between DES exposure and increased breast cancer risk for women who took the drug,^{91,92} as well as for their daughters who were exposed prenatally.⁹³

Some studies have looked at indirect markers of fetal estrogen exposure, mainly birth weight of infants. Higher birth weight is associated both with increased maternal estrogens during pregnancy and risk of breast cancer, especially pre-menopausal cancer, in later life.⁹⁴ Data from these studies do indicate that changes in the fetal environment, resulting in increased exposure to estrogens or estrogen-mimicking chemicals, lead to higher incidence of breast cancer in adulthood.

A long-term study of pregnant Dutch women living in a period of severe famine during 1944–1945 showed that exposure to famine—especially during the first trimester—also led to a several-fold increase in breast cancer rates in daughters.⁹⁵ Although the mechanisms underlying this effect are not understood, the results support the notion that prenatal events can have profound effects on subsequent risk for breast cancer.

There is at least one study that has more directly examined the effects of environmental contaminants at around the time of birth on development of breast cancer in women. Polycyclic aromatic hydrocarbons (PAHs) are products of incineration found in air pollution, vehicle exhaust (particularly diesel), tobacco, smoke, and grilled foods. They have been shown to be carcinogenic and to increase risk for breast cancer by altering estrogen-mediated cell systems.⁹⁶ A recent study in western New York examined air-monitoring records from 1959 to 1997 to establish PAH levels in residential areas. This case-control study of 3,200 women (ages 35–79 years) showed that exposures to high levels of PAHs at the time of their birth were associated with an increased risk of post-menopausal breast cancer decades later.⁹⁷

Data from animal studies support the notion that prenatal exposures to environmental chemicals can increase the risk of breast cancer. Bisphenol A (BPA) is a chemical found widely in food packaging and containers. In a recent study, 95% of people tested had measurable levels of BPA in their urine.⁹⁸ Fetal exposure of mice to low-dose BPA changed the timing of DNA synthesis in the mammary epithelium and stroma, increased the number and extension of terminal ducts and terminal end buds (i.e., the structures where cancer arises), and increased the sensitivity of the mammary gland to estrogens during postnatal life.^{99,100} These results suggest that alterations in mammary gland structure that are observed in puberty and adulthood in perinatally exposed animals have their origins in fetal development. These data are particularly important because very low doses of BPA resulted

in abnormal mammary gland development, and the effects were found in the absence of co-treatment with any other cancer promoter. According to Markey et al., these findings “strengthen the hypothesis that in utero exposure to environmental estrogens may predispose the developing fetus to mammary gland carcinogenesis in adulthood.”¹⁰¹

Most importantly, prenatal exposures of mice to BPA led to preneoplastic (intraductal hyperplasias) and neoplastic (carcinoma in situ) lesions in mammary glands that were visible at the onset of puberty.¹⁰² Following brief post-pubertal exposure to a known carcinogen, adult animals that also had been exposed prenatally to low doses of BPA developed more precancerous and cancerous abnormalities in their mammary tissues.¹⁰⁰ Similarly, laboratory studies have shown that prenatal exposures to either the dioxin TCDD^{103–105} or a breakdown product of the commonly used herbicide atrazine¹⁰⁶ alter subsequent mammary gland development in ways that predispose rats to develop mammary cancers as adults. These studies demonstrate a common critical window of prenatal exposure for these persistent effects in the adult mammary gland.

Together these data demonstrate that in both women and in relevant rodent models, exposure during gestation can lead to aberrations in development of breast/mammary tissues in ways that greatly increase the risk for developing breast/mammary cancer later in life.

Childhood and Adolescent Exposures. It is difficult to identify environmental chemicals to which women were exposed during childhood and adolescence. However, a recent study shows that exposure to the now banned, but once widely used, pesticide DDT during childhood or early adolescence led to a fivefold increase in breast cancer risk before age 50.¹⁰⁷

There are also numerous studies demonstrating that exposure to ionizing radiation,^{105–109} and possibly alcohol consumption, diet, and lack of physical exercise during childhood and adolescence could play a role in breast carcinogenesis. The few studies examining exposures to environmental chemicals in animal models are inconclusive, and peri-pubertal effects of most chemicals have not been studied.⁸⁷

The connection between childhood or adolescent exposures to radiation and breast cancer is clearer. In women, links between radiation exposure and breast cancer have been confirmed in atomic bomb survivors.^{110,111} Rates of breast cancer were highest among women who were younger than age 20 when the United States dropped atomic bombs on Hiroshima and Nagasaki, with an reported relative risk (RR) of 13.0 for women whose cancer was diagnosed before the age of 35, and a doubling of diagnoses of breast cancer later in life for women exposed before age 20.¹¹¹ Following the accidental contamination in 1986 by massive

amounts of radiation in the area surrounding Chernobyl in the former Soviet Union, increases in breast cancer have been observed in women living in surrounding areas.¹¹² The association was strongest in women at higher exposure levels who were premenopausal at time of exposure (RR = 2.24; 95% CI = 1.51–3.32),¹¹² although is still too early to learn of the physiological ramifications of the accident on women who were girls or teens at the time of the accident.

Moorin-Doody et al. found that adolescent girls whose treatment for scoliosis was monitored with repeated X-rays to their backs had increased rates of breast cancer compared to women who did not receive multiple X-rays (adjusted RR = 2.70; 95% CI = –0.02–9.3).¹¹³ Similar exposures of older women with scoliosis did not have the same cancer-promoting effect.

X-ray treatment of children, adolescents and very young adult women with Hodgkin's lymphoma led to significant increases in breast cancer risk in later adulthood, with most of the cancers developing in the area that had previously been irradiated.¹¹⁴ Girls and adolescents treated with radiation to combat non-Hodgkin's lymphoma had a similar increase in rates of breast cancer several decades later.¹¹⁵ For women who had repeated fluoroscopic exposures while being treated as young girls for tuberculosis, younger age and increasing dose of radiation exposure were both associated with a statistically significant increase in breast cancer incidence in adulthood.¹¹⁶ When women who had been treated with radiation for enlarged thymus glands during infancy were compared with their non-treated sisters, a significantly higher incidence of breast cancer was found among the women who had received early X-ray treatments (RR = 3.61; 95% CI = 1.8–7.3).¹¹⁷ And a recent study has demonstrated that women who were exposed to dental X-rays during early childhood (starting before age 10) without the consistent use of protective lead aprons also show an increased risk (RR = 1.81; 95% CI = 1.13–2.90) of breast cancer diagnosis.¹¹⁸

Regarding diet and later risk for breast cancer, few if any reliable and replicable effects have been found looking across all age ranges.³ Still, there is substantial evidence that high dietary intake during adolescence of animal fats, but not vegetable fats,^{119,120} may lead to increased breast cancer incidence later in life. Possible protective effects of genistein or soy intake are strongest when the compounds were taken as regular parts of diet during puberty (in rats)¹²¹ or adolescence (in girls).¹²² Similarly and with clearer evidence, physical activity during adolescence is associated with a decrease in later breast cancer risk,¹²³ reinforcing the impact of metabolic and related hormonal status during this stage on later risk for breast cancer.

In addition to ensuring opportunities for proper exercise and a balanced healthful diet, we need more research to better understand the impact of children's exposures on susceptibility to breast cancer and other dis-

eases. In the meantime, advocates and policy makers should err on the side of precaution to minimize and, where possible, eliminate exposures to the damaging effects of ionizing radiation and environmental toxicants.

BREAST CANCER OR BREAST CANCERS?

There are several different presentations of breast cancer and increasing sophistication in differentiation among subtypes of the disorder. Sometimes the site of cancer origin within the breast (duct vs. lobe) is compared. Of the two most common forms of breast cancer, ductal cancer is more common (about 85% of breast cancers), but the lobular form may be more difficult to diagnose, leading on average to larger, more aggressive tumors at the time of diagnosis.¹²⁴ Another type of breast cancer, inflammatory breast cancer, is a relatively rare (1–6% of cases in the U.S., although incidence is much higher in Northern Africa) but exceedingly aggressive form of the disease that presents with rapid swelling, reddening and irritation of the breast tissue with or without an underlying solid breast lump.¹²⁵

The tumor types described above are all forms of invasive breast cancer, or cancer that has spread beyond the confines of the ducts or lobes of the mammary system. Many research studies only look at women with invasive breast cancer. On the other hand, with increased use of mammography over the past two decades, diagnoses of ductal carcinoma in situ (DCIS) have increased 4–5 times. DCIS is diagnosed when there is the appearance of abnormal cells contained within the walls of the ducts of the breast. At the time of diagnosis, DCIS is not life-threatening. However, some DCIS will eventually transform into invasive cancer and, at present, clinicians cannot predict with reliability in which women this will happen. As a result, many women with DCIS are treated as though they have an early form of invasive cancer, undergoing both surgical and/or radiation treatments.¹²⁶

Breast cancers often are distinguished by age at diagnosis, with age 50 generally used as an arbitrary marker for the transition from premenopausal to postmenopausal stages of a woman's reproductive life. Sometimes more precise information about menopausal status is gleaned either from the woman or from her medical records. Menopausal status is important because it marks the gradual but important downward shift in secretion of estrogens in the body. As we have seen, total exposures to estrogens, estrogen mimics and endocrine system disruptors—from any of a number of different sources—have been associated with increased risk for breast cancer later in life.

A different set of breast cancer subtypes has recently been established. Distinguished on the basis of a number of biological markers (genes or proteins found in cells that have been associated with mechanisms

TABLE 1 Breast Cancer Molecular Markers

Molecular Market	Description	Biological Significance
Estrogen receptor ER+ ER-	Protein needed for many cellular actions of estrogens.	Actions can be blocked by anti-estrogens (e.g., tamoxifen).
Progesterone receptor PR+ PR-	Protein that is a product of activation of the estrogen receptor.	Necessary for cellular actions caused by progesterone.
HER2 HER2+ HER2-	Cell membrane protein that is important in translation of messages leading to increased cell growth and proliferation.	Actions can be blocked by drugs (e.g., Herceptin).
<i>BRCA1, BRCA2</i>	Genes that were identified in the early 1990s as important in the inherited transmission of breast cancer in a minority (5 to 10 percent) of cases.	Encode proteins involved in the repair of DNA mutations.
Other genes <i>p53</i> <i>FGFR2</i> et al.	Genes that are involved in the encoding of proteins that alter cell pathways involved in the development of breast cancer.	Mutations may influence susceptibility to environmental, hormonal or other factors.

underlying breast cancer; see Table 1), these include basal, HER2 over-expression, luminal A, luminal B, normal, and unclassified.^{127,128} The basal subtype (ER negative, PR negative, HER2 negative) is found in only about 15% of breast cancers but has been shown to be aggressive, unresponsive to treatment, and ultimately indicative of a poor prognosis.^{129,130} The Carolina Breast Cancer study (2006) found a significant increase in this aggressive subtype of the disease in premenopausal African American women, a probable contributor to the poorer prognosis of women in this category relative to others of the same age but different racial/ethnic backgrounds.¹³¹

Finally, it is important to acknowledge that approximately 1% of all diagnoses of breast cancer are in men. The scientific literature indicates that many of the risk factors for men are similar to those for women, including a combination of genetic, hormonal and environmental factors.¹³² Male breast cancer has been linked to occupational exposures to gasoline and vehicle combustion, PAHs, EMF and some industrial solvents.^{127,128,132,133} Nevertheless, nearly all scientific research has been directed toward understanding breast cancer and its causes in women or female animals. It is hoped that a better understanding of the complex causes underlying female breast cancer will also illuminate the factors influencing its development in males.

EVIDENCE LINKING ENVIRONMENTAL FACTORS AND BREAST CANCER

Hormones and Endocrine-Disrupting Compounds

Estrogens and Progestins. Extensive exposures to estrogens and progestins, most notably to the estrogen estro-

diol, have been implicated in increased risk for breast cancer.⁸⁰ It is believed that many environmental chemicals exert their carcinogenic effects by mimicking or disrupting hormone-regulated pathways, especially estrogen. Breast cancer in men also implicates estrogen as a contributing factor. Although breast cancer is rare in men, those who develop the disease have been found to have higher than normal levels of estrogen, which originates from secretions of the testes or adrenal glands.¹³⁴

Hormones like estradiol and progesterone are lipophilic and accumulate in fatty tissues of the body. Breasts are composed primarily of fat and therefore are repositories both for natural steroid hormones as well as for many lipophilic environmental contaminants. Breast tissue also contains several enzymes including aromatase, which converts local androgenic hormones to estrogens within the breast. The activity of aromatase is elevated in breast cancer tissue as compared to normal breast tissue.¹³⁵

Hormone Replacement Therapy (HRT) and Oral Contraceptives. Over the past several decades, pharmaceutical companies have developed a variety of mixtures of natural and synthetic ovarian hormones used mainly for contraception or post-menopausal hormone replacement therapy (HRT). The International Agency for Research on Cancer (IARC) has listed estrogens as known human carcinogens since 1987, and their component hormones since 1976.¹³⁶ In 2002, the National Toxicology Program (NTP) added HRT and estrogens used in oral contraceptives to the list of known human carcinogens.¹³⁷

These classifications reflect scientific evidence linking steroidal estrogens to increased cancer risk.¹³⁸ Data

now show that when a woman's natural estrogens are supplemented by oral contraceptives and/or HRT, her risk of breast cancer increases.^{13,140,141} Women who with a history of oral contraceptive use who receive HRT face an elevated breast cancer risk.^{142,143} Shantakumar et al. found the effect to be most pronounced for premenopausal women who have taken both oral contraceptives and hormone therapy (OR = 2.59; 95% CI = 1.50–4.46).¹⁴⁴

Hormone Replacement Therapy (HRT). In 2002, the Women's Health Initiative (WHI) study, designed to explore the benefits and risks of combined estrogen plus progestin HRT in postmenopausal women, was halted before the end of study period. Of more than 16,000 women ages 50–79, half took Prempro, a combination of estrogen plus progestin. The other half took a placebo. Researchers halted the WHI study after five years because they saw a 26% increase in the risk of breast cancer in the intervention group, in addition to significant increases in the risk of heart disease, stroke and blood clots.¹⁴⁵ Considering the 42% of women who had withdrawn from the study before the five year point, the relative risk of breast cancer among HRT-treated women increased from 26% to 49% (43 women with breast cancer versus 30 women per 10,000 person-years).

More recent analyses clarify that the increased risk of breast cancer in the WHI study is found for women taking the combined estrogen-progestin formula, but not for those women taking estrogen-only HRT supplements.¹⁴⁶

In 2003, Swedish researchers halted a study of HRT in women with a history of breast cancer. Originally planned as a five-year study, the Swedish trial was stopped after two years because women taking HRT had three times the rate of recurrence or new tumors compared to women who received other treatments for menopausal symptoms.¹⁴⁷

Also in 2003, researchers in the Million Women Study (MWS) in the United Kingdom reported that the use of all types of postmenopausal HRT significantly increased the risk of breast cancer.¹⁴⁸ The risk was greatest among users of estrogen-progestin combination therapy. The study enrolled more than 1 million women ages 50–64. Researchers estimated that women who used estrogen-progestin HRT for 10 years were almost four times as likely to develop breast cancer as women who used estrogen-only HRT (19 additional breast cancers per 1,000 women compared to five per 1,000). Use of HRT by women ages 50–64 in the U.K. over the past decade has resulted in an estimated 20,000 extra breast cancers, 15,000 of them associated with estrogen-progestin combination.

Several other studies have confirmed that HRT increases risk of breast cancer in postmenopausal women. Examination of cancer histology in women taking combined HRT at the time of diagnosis reveals

an increased presentation of breast cancer of lobular origin,^{146,147} but also of cancers with low proliferation rates (mitotic indices) and favorable prognostic outcome.^{150,151} For example, Borgquist et al. reported a significant increase (RR = 3.01; 95% CI = 2.35–3.84) of breast cancer incidence in their population-based study of peri- and postmenopausal women taking combined HRT. Use of HRT was associated with tumors of lobular origin (RR = 3.48; 95% CI = 1.99–6.10), grade 1 (RR = 4.46; 95% CI = 2.79–7.13), and low mitotic index (RR = 4.35; 95% CI = 2.99–6.34).¹⁵⁰

Oral Contraceptives. Numerous studies have shown an increased risk of breast cancer in women using oral contraceptives.^{152–156} The risk is greatest among current and recent users, particularly those with a history of more than five years' use, young age at oral contraceptive initiation, premenopausal women, those with a family history of breast cancer,¹⁵⁷ and possibly for those with *BRCA1* or *BRCA2* mutations.^{158,159} As with HRT, current use of oral contraceptives has been associated with an increase in breast tumors originating in the lobular tissue, (OR = 2.6; 95% CI = 1.0–7.1)¹⁵⁵ as well as with the estrogen receptor negative (RR = 3.56; 95% CI = 1.8–7.1) (no or low estrogen receptor) profile of the disease.¹⁵³

Grabrick et al. examined possible effects of oral contraceptive use on later risk for breast cancer in Hispanic and non-Hispanic white women. Statistically, Hispanic women have somewhat lower rates of breast cancer than do white women, and they are more likely to have ER- breast cancer. However, use of oral contraceptives in the past five years has led to significant increases in breast cancer incidence in both groups. The effect was magnified for women of both groups when OC use continued for more than 20 years (OR = 2.23; 95% CI = 1.17–4.25 for ER- tumors).¹⁶⁰

Postmenopausal women who used oral contraceptives for eight or more years, but who have discontinued use for at least a decade, show no significant increase in breast cancer rates.¹³⁹

Diethylstilbestrol. Between 1938 and 1971, doctors prescribed DES for millions of pregnant women to prevent miscarriages. The drug was banned when daughters of women who took the drug were found to have higher rates of an extremely rare vaginal cancer compared to those who were not exposed to DES in the womb.^{161,162,163} Research indicates that DES exposure is also associated with an increased risk of breast cancer in the women who took it during the 1950s.^{91,92}

In a follow-up study of daughters who were exposed prenatally to DES, a nearly two-fold increase in breast cancer risk was observed in women older than age 40.^{93,164} An even greater effect was found for women over the age of 50, although there were still relatively few of the daughters who had yet reached that age.¹⁶⁴

Estrogens and Placental Hormones (Progestins) in Personal Care Products. Placental extracts, probably with high concentrations of progesterone⁶¹ and estrogenic chemicals, are sometimes used in cosmetics and hair care products, particularly products marketed to women of color. The addition of hormones and extracts is advertised as promoting growth and thickness of hair. However, research indicates that use of these products in infants and children may also be linked to precocious puberty or early sexual maturation.^{165–167} Early puberty is a risk factor for breast cancer later in life.¹⁶⁸ Some researchers have recently proposed that use of these hormone-altered products might be contributing to the increased incidence of breast cancer, especially among young African American women.¹⁶⁹

Phytoestrogens (Plant Estrogens). The prevailing evidence against synthetic estrogens must also be understood alongside evidence about the effects of plant estrogens (phytoestrogens). Foods such as whole grains, dried beans, peas, fruits, broccoli, cauliflower and especially soy products are rich in phytoestrogens. Although scientific evidence suggests that plant-based estrogens offer nutritional benefits and are associated with healthy diets, the data are conflicting as to whether the plant estrogens are beneficial, harmful, or neutral when it comes to breast cancer risk.^{170,171}

Some research indicates that phytoestrogens may counteract the effects of synthetic xenoestrogens. Adding soy products to women's diets has led to lower levels of harmful estrogens in their bodies.¹⁷¹ Some human and laboratory studies suggest that long-term consumption of plant-based estrogens, especially during childhood and adolescence, may help reduce a woman's later risk of breast cancer.¹⁷²

On the other hand, Japanese researchers reported that genistein, a type of phytoestrogen found in most soy products, and daidzein, another phytoestrogen, and their metabolites cause oxidative DNA damage, which is thought to play a role in tumor initiation.¹⁷³ Other data suggest that these two soy-based phytoestrogens may have opposing effects on the efficacy of the breast cancer drug, tamoxifen.^{174,175} Overall, the evidence on whether dietary phytoestrogens increase or decrease breast cancer risk in adult women remains incomplete and inconclusive. It may be unwise for women, especially those with estrogen-receptor positive breast tumors, to increase their phytoestrogen intake.

Xenoestrogens and Other Endocrine-disrupting Compounds (EDCs)

A wide variety of chemicals including plastic additives, industrial solvents, pesticides and herbicides, as well as chemical byproducts of combustion or industrial manufacturing processes, can mimic or alter the activities of

the natural hormones, especially the estrogens. These xenoestrogens are members of a larger class of synthetic chemicals known as endocrine disruptors, which mimic or disturb the activity of a much wider group of hormones, including the androgens, adrenal hormones, and thyroid hormones. The term "endocrine disruptor" is used to reflect the wide range of effects these compounds may have on the endocrine system.

The effects of endocrine disruptors, including xenoestrogens, on reproduction and development have been well-established in a number of wildlife species.¹⁷⁶ Data from humans are more controversial and less conclusive. Given the pervasive presence of many of these chemicals in the physical environment, alone and in mixtures, it is difficult to determine clear relationships between individual chemicals and their effects on risk for cancer or other disorders.

To date, neither the NTP nor IARC have classified most endocrine disruptors as carcinogens in humans, reflecting controversies in the scientific literature, considerable pressure from industry, and failure of the scientific communities and regulatory agencies to agree on methodologies and criteria for classification of these chemicals. For example, the U.S. EPA and other regulatory agencies are still struggling to determine appropriate experimental tests for measuring the hormonal properties of environmental chemicals.¹⁷⁷

Despite the lack of formal classification of many xenoestrogens as chemicals that increase risk for breast cancer, a substantial body of peer-reviewed scientific literature implicates many of these chemicals in the current high rates of the disease. These data come primarily from laboratory studies with animal or cell culture models. A growing body of human epidemiological data supports these lab studies, and research suggests that the primary mechanism by which these chemicals may exert effects on breast cancer risk involve mimicking or disruption of estrogen pathways.¹⁷⁸

In 1991, Soto et al. found that a chemical leaching from polystyrene laboratory tubes was causing breast cancer cells to grow in vitro, even though no estrogens had been added to the culture. Subsequent investigation identified the substance leached as p-nonylphenol, an additive commonly used in plastics, which behaves like a natural estrogen.¹⁷⁹ This landmark discovery generated widespread interest in what we now call xenoestrogens¹⁷⁸—synthetic agents that mimic the actions of estrogens.

Subsequently, Soto et al. identified the pesticides endosulfan, toxaphene and dieldrin as xenoestrogens because they caused breast cancer cells to proliferate in culture.¹⁸⁰ In the last decade and a half, more chemicals have been added to the list of endocrine disruptors or potential disruptors. In 2004, the Commission of the European Communities identified 147 such substances.¹⁸¹ (See Appendix 2 for a list of selected endocrine disruptors and their uses.)

TABLE 2 Selected Compounds Linked to Breast Cancer

	IARC			NTP		Endocrine Disrupting Compounds
	Known	Probable	Possible	Known	Reasonably Anticipated	
Hormones and Endocrine Disrupting Compounds						
<i>Estrogens and Progestins</i>						
Hormone Replacement Therapy (HRT) and Oral Contraceptives	X			X		
Diethylstilbestrol (DES)	X			X		
Estrogens and Placental Hormones (Progestins) in Personal Care Products	X			X		
<i>Xenoestrogens and Other Endocrine Disrupting Compounds (EDCs)</i>						
Dioxins	X			X		X
Persistent Organochlorines DDT/DDE and PCBs						
DDT/DDE			X	X		X
PCBs		X			X	X
Pesticides						
Triazine Herbicides: Atrazine						X
Heptachlor			X			X
Dieldrin and Aldrin						X
Some Other Pesticides						X
Polycyclic Aromatic Hydrocarbons (PAHs)		X			X	X
Tobacco Smoke: Active and Passive Exposures	X			X		X
Bisphenol A (BPA)						X
Alkylphenols						X
Some Metals	X			X		X
Phthalates						X
Parabens						X
Sunscreens (UV Filters)						X
<i>Growth Promoters Used in Food Production</i>						
Recombinant Bovine Growth Hormone (rBGH)/Recombinant Bovine Somatotropin (rBST)						X
Zeranol (Raigro)						X
Other Chemicals of Concern						
Benzene	X			X		
Other Organic Solvents		X			X	
Vinyl Chloride	X			X		
1,3-Butadiene		X		X		
Ethylene Oxide	X			X		
Aromatic Amines		X			X	X

An epidemiologic study conducted on Cape Cod, where nine of 15 towns have breast cancer rates 20% above the average rates for Massachusetts, has raised suspicions about exposure to synthetic estrogens in the environment and increased risk of breast cancer.¹⁸² Longer residence on Cape Cod is associated with increased risk of breast cancer; women who lived just five or more years on the Cape experienced a higher incidence rate, with the highest risk among women who had lived on the Cape for 25–29 years (OR = 1.72; 95% CI = 1.12–2.64). Suspected environmental exposures include pesticides and drinking water contaminated by industrial, agricultural and residential land use.¹⁸³

Researchers found synthetic estrogens in septic tank contents, groundwater contaminated by wastewater and in some private wells.¹⁸⁴ Researchers found 52 different hormonally active agents and mammary carcinogen compounds in air and 66 in dust, including phthalates, parabens, alkylphenols, flame retardants, PAHs, polychlorinated biphenyls (PCBs) and bisphenol A, in addition to banned and currently used pesticides.⁶²

In the following sections we address in more detail some of the most common xenoestrogens and endocrine-disrupting compounds, along with some of the evidence linking them to breast cancer.

Dioxins. Dioxins are formed by the incineration of products containing PVC, PCBs and other chlorinated compounds, as well as from industrial processes that use chlorine and from the combustion of diesel and gasoline.¹⁸⁵ One of the dioxins (2,3,7,8-tetra chlorodibenzo-para-dioxin [TCDD]) has been classified by IARC¹⁸⁶ and the U.S. EPA¹⁸⁷ as a known human carcinogen.

Dioxins break down very slowly and accumulate in the body fat of wildlife. People are exposed to dioxins primarily through consumption of animal products and human breast milk.^{185,188} Dioxin enters the food chain when vehicle exhaust or soot from incinerated chlorinated compounds falls on field crops later eaten by farm animals. It is then passed to humans through dairy and meat products. The body fat of every human being, including every newborn, is thought to contain dioxins.¹⁸⁸

There is a substantial decrease in the amount of dioxin remaining in a woman's breast fat tissue after she has breast fed because the chemicals have been passed on to her newborn via breast milk.¹⁸⁹ Although the presence of toxic chemicals in breast milk is potentially dangerous, the beneficial nutrients and immune system boosters that are transferred from mother to infant are thought to far outweigh the potential toxic transfers.⁶⁴

A recent follow-up study on women exposed to dioxins during a chemical plant explosion in 1976 in Seveso, Italy shows an association between dioxin and breast cancer.¹⁹⁰ Warner et al. found that a tenfold increase in TCDD levels in blood samples taken at the time of the explosion was associated with more than twice the risk of breast cancer (Hazard Ratio [HR] = 2.1; 95% CI = 1.0–4.6). Women who were children at the time of the accident are just beginning to reach the age when breast cancer is most likely to develop and researchers will continue to follow the Seveso women.

A retrospective mortality study in Germany examined deaths from cancer among people who had worked in a chemical factory in which they were exposed to high levels of TCDD. There was no increase in overall mortality from cancer for female workers, although there was a significant increase in deaths from breast cancer among those who worked in high exposure regions of the factory (SMR = 2.15).¹⁹¹

A number of laboratory studies have demonstrated that when looking at later changes in mammary cancer rates, the timing of exposures to dioxins matters. Although exposing animals to dioxins in adulthood may not affect cancer rates, earlier exposures may have profound effects. Several studies have shown that administration of dioxin (especially TCDD) to pregnant rats leads to structural abnormalities in the development of their pups' mammary tissues and higher incidence of tumors when the pups grow to adulthood.^{103–105,192}

Persistent Organochlorines: DDT/DDE and PCBs. Endocrine disruptor chemicals include dichloro-diphenyl-

trichloroethane (DDT), an organochlorine pesticide, and the polychlorinated biphenyls (PCBs), a large group of chemicals that were used in the manufacture of electrical equipment and numerous other industrial and consumer products. Both DDT and PCBs have been banned in the United States for three decades, yet both are still found in soil, riverbeds and dust particulates in homes.^{62,193} Due to historical overlap in exposures, and because of many similarities in structure and function, the two are often discussed together while their effects on disease have also been explored independently.

DDT/DDE. DDT was the first widely used synthetic pesticide. It is credited both with the eradication of malaria in the United States and Europe, and with devastating long-term effects on reproductive success in wildlife and adverse health effects in humans.¹⁹⁴ Although banned for agricultural use in many countries, DDT is still used for malaria control in 17 nations.¹⁹⁵ Because of its continued use and its persistence in the environment, DDT is found worldwide. Most animals, including humans, ingest DDT-contaminated foods and retain the chemical and its main metabolite, DDE. DDT and DDE are still found in the breast fat of humans and animals,¹⁹⁶ in human breast milk, and in placenta.^{67,197}

Epidemiological data are mixed regarding the effects of DDT/DDE on breast cancer risk. One study from the Long Island Breast Cancer Study Project did not find an association between DDT/DDE (or PCBs) and breast cancer.¹⁹⁸ Like many such studies, however, this project measured contaminant levels near the time of breast cancer diagnosis, without regard to possible exposures during critical early periods of breast development, and did not consider the effect of chemical mixtures or assess key metabolites.

Enoch et al. used women's year of birth as a proxy for historical exposures and measured blood DDT levels at the time the women gave birth. Results showed that exposure to DDT during childhood and early adolescence (<14 years) was associated with a fivefold increase in risk of developing breast cancer before the age of 50. As the authors note, "Many U.S. women heavily exposed to DDT in childhood have not yet reached age 50. The public health significance of DDT exposure in early life may be large."¹⁰⁷

Laboratory studies have found the estrogen-like form of DDT enhances the growth of estrogen-receptor positive (ER+) mammary tumors.^{199,200} The percentage of breast tumors in the United States that are ER+ rose from 73% in 1973 to 78% in 1992. This change corresponds to the period when women exposed to DDT as young girls were expected to be exhibiting environmentally altered incidence in breast cancer related to DDT exposure.²⁰¹ Woolcott et al., looking at chemical levels in breast adipose tissue, did not find an associa-

tion of DDT/DDE with ER+ tumors. However, data from this study indicated a significant association of higher concentrations of these compounds in breast tissue with tumors that were more aggressive and had poorer prognoses (OR = 2.40; 95% CI = 1.0–5.4).²⁰²

PCBs. Although the EPA banned the use of PCBs in new products in 1976, as many as two-thirds of all insulation fluids, plastics, adhesives, paper, inks, paints, dyes and other products containing PCBs manufactured before the ban remain in daily use. The remaining one-third has been discarded, which means that these toxic compounds eventually made their way into landfills and waste dumps.²⁰³

Levels of PCBs were high before being banned in the U.S., but generally their presence in human tissues has decreased slowly over the past three decades.²⁰⁴ Exposures were high between childhood and young adulthood for many women who are now facing a diagnosis of breast cancer. Choi et al. found that PCB levels in neonatal cord serum correlated with distance of mother's residence from a superfund site; levels were lower in infants born after site remediation.²⁰

The more than 200 individual PCBs are classified into three types based on their effects on cells. One type acts like an estrogen. A second type acts like an anti-estrogen. A third type appears not to be hormonally active, but can stimulate enzyme systems of animals and humans in a manner similar to certain drugs (such as phenobarbital) and other toxic chemicals.²⁰⁶ Additionally, hydroxylated metabolites of PCBs alter the expression of genes involved in hormone synthesis, indicating that these compounds may act as endocrine disruptors through a route not directly involving the estrogen receptor.²⁰⁷

Most studies have looked at total PCB levels without identifying individual types. A few studies, however, have looked at relationships between cancer status and particular PCBs. For example, in a 2004 case-control study, Charlier et al. found significantly higher total blood levels of PCBs, particularly PCB 153, in women with breast cancer than in presumably healthy women (1.63 ± 1.26 ppb vs. 0.63 ± 0.78 ppb; $p < 0.0001$).²⁰⁸ PCB 153 has been shown to exhibit estrogen-like activity in animal and in vitro studies. Aronson et al. measured several types of PCBs, along with DDE, in breast biopsy tissue. They found that "ORs were above two in the highest concentration categories of PCB congeners 105 and 118, and the ORs for these PCBs increased linearly across categories (p s for trend ≤ 0.01)."²⁰⁹ Interestingly, none of these four PCBs were shown to have estrogenic activity in a study using MCF-7 cell proliferation to test for estrogenicity of compounds.²¹⁰

Another report has implicated PCBs in breast cancer recurrence among women with nonmetastatic breast cancer. The study found an increased risk of recurrent breast cancer in women with the highest levels of total

PCBs (RR = 2.91; 95% CI = 1.0–8.2), as well as of PCB 118 (RR = 4.0; 95% CI = 1.3–4.9), in their adipose tissues.²¹¹

Some studies have shown no link between PCB exposure and breast cancer.²¹² However, more study is needed to determine the effect of PCB exposure on breast carcinogenesis in specific populations. For example, researchers evaluating data from the Nurses' Health Study originally concluded that exposure to these chemicals was unlikely to explain high breast cancer rates.²¹³ In 2002, new evidence regarding variations in individual susceptibility due to genetic differences prompted a call for additional studies.⁸⁴

In vitro studies of human breast cancer cells have demonstrated that some specific types of PCBs promote the proliferation of breast cancer cells in culture by stimulating estrogen receptor (ER) mediated pathways^{214,215} and the activation of key enzymes and cellular changes that are characteristic of transformation of cells to a malignant state.²¹⁶

Pesticides

A 2006 report from the Long Island Breast Cancer Study Project demonstrated that self-reported lifetime use of residential pesticides was associated with an increase in risk for breast cancer. The increase was found for women who had reported use of pesticides in the aggregate (OR = 1.39; 95% CI = 1.15–1.68), as well as specifically for use of lawn (OR = 1.48; 95% CI = 1.20–1.82) and garden (OR = 1.58; 95% CI = 1.12–2.22) pesticides, although there were no relationships perceived doses of exposures and risk of cancer.²¹⁷ These results are important because they address exposures to chemicals in the course of ordinary life, with all the complexities of mixtures and multiple sorts of uses. Many other studies focus on single chemicals or classes of chemicals, and the results are often contradictory depending on length and timing of exposures, types of chemical being studied and so forth. Despite that, many pesticides and herbicides have been labeled as human or animal carcinogens (see Appendix 1). Many are also found in water supplies,²¹⁷ samples of air and dust from homes.⁶²

Triazine Herbicides: Atrazine. Triazine herbicides are the most heavily used agricultural chemicals in the United States. Triazines include atrazine, simazine, propazine and cyanazine. Although all have been shown to cause mammary cancer in laboratory rats,²¹⁸ there is relatively little scientific data exploring the relationship between simazine or cyanazine and breast cancer. The literature on atrazine is much more extensive.

Dupont, the maker of cyanazine, negotiated with the EPA a gradual phase-out of the pesticide beginning in 1996.²¹⁹ Supplies of cyanazine that remained after December 1999 could be used through the end of 2002. Atrazine was banned in the European Union in

2005 because of its high presence in drinking water, its demonstrated harmful effects on wildlife and its potential health effects in humans. Atrazine is still approved for use in the United States. More than 75 million pounds of atrazine are applied annually in the U.S., primarily to control broadleaf weeds in corn and sorghum crops in the Midwest.²²⁰

Elevated levels of atrazine are found each spring and summer in both drinking water and ground water in agricultural areas.^{221–223} High levels of triazines (primarily atrazine) in contaminated waters have been associated with an increased risk of breast cancer.²²⁴ Atrazine is a known endocrine disruptor, causing dramatic damage to reproductive structures in frogs.²²⁵ Research in rodents has shown that atrazine exposure disrupts pituitary-ovarian function, including a decrease in circulating prolactin and luteinizing hormone levels, changes that contribute to the effects of this chemical on increases in mammary tumors.^{218,226}

Recent *in vitro* data suggest that one mechanism by which atrazine exerts its endocrine disrupting effects is by increasing the activity of the enzyme aromatase.^{227,228} Aromatase catalyzes the conversion of testosterone and other androgens to estrogens, including estradiol. Androgens are found naturally in women, although at lower levels than in men. The production of estrogens through the aromatase pathway, however, is of sufficient importance in the etiology of breast cancer that one class of breast cancer drugs aims specifically to block the activity of aromatase.²²⁹

Exposure to atrazine during gestation delays development of the rat mammary gland in puberty, widening the window of sensitivity to breast carcinogens.²³⁰ Similarly, exposure of rats late in pregnancy to a mixture of commonly formed metabolites of atrazine also leads to persistent changes in mammary gland development in their pups exposed during gestation. These abnormalities persist into adulthood.¹⁰⁷

Heptachlor. Heptachlor is an insecticide that was widely used in the United States throughout the 1980s, especially for termite control. In 1988, the U.S. EPA restricted use of heptachlor to certain applications for controlling fire ants, but agricultural use continued until 1993 because growers were allowed to use existing stocks.²³¹ Heptachlor use was particularly high in Hawaii, where it was used extensively on pineapple crops and consequently contaminated both local agricultural crops and dairy supplies. Breast cancer rates in Hawaii have increased dramatically for women of all ethnic groups over the past four decades.²³²

Heptachlor still contaminates both soil and humans. Its breakdown product, heptachlor epoxide (HE) is known to accumulate in fat, including breast tissue. Levels are highest in women ages 20 and older, but HE is also found in the bodies of adolescents 12 to 19 years old,⁵¹ and in eight of 10 samples of umbilical cord

blood from newborn infants.²³³ High levels of HE in breast milk²³⁴ and fat tissue from breast biopsies²³⁵ have been shown to be associated with increased incidence of breast cancer.

Although HE does not act like estrogen, it affects the way the liver processes estrogen by allowing levels of circulating estrogens to rise, thereby increasing breast cancer risk. HE also has been shown to disrupt cell-to-cell communication in human breast cells in tissue culture²³⁶ and to increase production of nitric oxide, a chemical that is found naturally in cells and is known to cause damage to DNA.²³⁵

Dieldrin and Aldrin. From the 1950s until 1970, the pesticides dieldrin and aldrin (which breaks down to dieldrin, the active ingredient) were widely used for crops including corn and cotton. Because of concerns about damage to the environment and, potentially, to human health, the U.S. EPA in 1975 banned all uses of aldrin and dieldrin except in termite control; the agency banned these pesticides altogether in 1987.²³⁷ Thus, most of the human body burden of this chemical comes either from past exposures or lingering environmental residues. Dieldrin has exhibited estrogenic activity during *in vitro* assays.

Hoyer et al. showed a clear relationship between breast cancer incidence and dieldrin in their examination of a rare bank of blood samples taken from women before the development of breast cancer.²³⁸ During the late 1970s and early 1980s, blood samples were taken from approximately 7,500 Danish women age 30–75. Researchers detected organochlorine compounds in most of the 240 women who were diagnosed with breast cancer prior to the study's publication in 2000. They found dieldrin in 78% of the women who were later diagnosed with breast cancer. Women who had the highest levels of dieldrin long before cancer developed had more than double the risk of breast cancer compared to women with the lowest levels. This study also showed that exposure to dieldrin correlated with the aggressiveness of breast cancer: higher levels of dieldrin were associated with higher breast cancer mortality.²³⁹

Like many other pesticides found in the environment, dieldrin has been shown to be an endocrine disruptor, both by stimulating estrogen-regulated systems and by interfering with androgen-regulated systems. Addition of dieldrin to human breast cancer (MCF-7) cells *in vitro* can stimulate their growth and proliferation.^{180,240}

Other Pesticides. A case-control study of 128 Latina agricultural workers newly diagnosed with breast cancer in California identified three pesticides—chlordane, malathion, and 2,4-D—associated with an increased risk of the disease. Scientists found that the risks associated with use of these chemicals were higher in young women and in those with early-onset breast cancer than in unexposed women.⁵³

Engel et al. studied the association between pesticide use and breast cancer risk in farmers' wives in the U.S. National Cancer Institute's Agricultural Health Study. This large prospective cohort study enrolled more than 30,000 women in the states of Iowa and North Carolina. Researchers found evidence of increased risk of breast cancer in women whose husbands used 2,4,5-trichlorophenoxy propionic acid (2,4,5-TP) (RR = 2.0; 95% CI = 1.2–3.2); a non-significant association was found for dieldrin and captan. Risk was also modestly elevated in women whose homes were closest to areas of pesticide application (RR = 1.7; 95% CI = 1.0–2.9).²⁴¹

Alexander et al. found that children ages 4–11 of farmers using 2,4,5-TP on their farms had high levels of the pesticide in their urine samples soon after the chemical had been applied to the fields.²⁴²

Polycyclic Aromatic Hydrocarbons (PAHs). PAHs are ubiquitous byproducts of combustion, from sources as varied as coal and coke-burners, diesel-fueled engines, grilled meats, and cigarettes. PAH residues are often associated with suspended particulate matter in the air, and inhalation is a major source of PAH exposure.⁹⁷ In the Silent Spring Institute study of environmental contaminants in house dust, three PAHs (pyrene, benzoanthracene and benzopyrene) were found in more than three-quarters of the homes tested.⁶²

Like many other environmental chemicals that are associated with breast cancer risk, PAHs are lipophilic and are stored in the fat tissue of the breast.²⁴³ PAHs have been shown to increase risk for breast cancer through a variety of mechanisms. The most common PAHs are weakly estrogenic.²⁴⁴ However, the major receptor-directed pathway is a different one, with PAHs associating with a protein called the aryl hydrocarbon receptor (AhR), initiating a series of cell changes that lead to altered cell signaling and ultimately to increases in DNA mutations.^{97,245} PAHs can also be directly genotoxic, meaning that the chemicals themselves or their breakdown products can directly interact with genes and cause damage to DNA.²⁴⁶

Several epidemiological studies have implicated PAH exposure in increased risk for breast cancer. One of the studies from the Long Island Breast Cancer Study Project found that women with the highest level of PAH-DNA adducts had a 50 % increased risk of breast cancer. PAH-DNA adducts are indicators of problems in DNA repair in cells, one of the early hallmarks of tumor development.²⁴⁷ In an earlier report, researchers explored the presence of PAH-DNA adducts in breast samples taken from women diagnosed with cancer as compared with those diagnosed with benign breast disease. Cancerous samples were twice as likely to have PAH-DNA adducts as were benign samples.²⁴⁸

Occupational exposure studies have looked at workers exposed regularly to gasoline fumes and vehicular

exhaust, major sources of PAHs (as well as benzene). These occupational exposures are associated with an increased risk of breast cancer for pre-menopausal women²⁴⁹ and also for men. In the case of male breast cancer, PAHs may specifically increase the risk of breast cancer in men carrying a *BRCA1* or *BRCA2* mutation.¹²⁸

Calafat et al., in case-control study in western New York, found that very early life exposure (around the time of birth) to high levels of total suspended particulates, a proxy measure for PAH levels, is associated with increased risk of breast cancer in post-menopausal women.⁹⁸

Tobacco Smoke: Active and Passive Exposures. Tobacco smoke also contains PAHs, which may explain a potential link between increased breast cancer risk and both active and passive smoking. Tobacco smoke contains hundreds of other chemicals,²⁵⁰ including three known human carcinogens (benzene, vinyl chloride, and polonium-210,²⁵¹ a radioactive element), as well as toluene and 1,3-butadiene, both of which are known to cause mammary tumors in animals.

Researchers at Japan's National Cancer Center recently reported the results of a study involving 21,000 women ages 40–59. They found that risk of breast cancer was elevated in pre-menopausal women who were either active smokers (RR = 3.9; 95% CI = 1.5–9.9) or exposed to environmental tobacco smoke (RR = 2.6; 95% CI = 1.3–5.2).²⁵² A large study of California teachers revealed an increased risk of breast cancer among smokers, particularly those who began smoking during adolescence (HR = 1.17; 95% CI = 1.05–1.30), at least five years before their first full-term pregnancy (HR = 1.13; 95% CI = 1.00–1.28), or who were long-term or heavy smokers (HR = 1.32; 95% CI = 1.10–1.57).²⁵³ Several earlier studies also suggest that women who begin smoking cigarettes as adolescents face increased risks of breast cancer.^{254–258} The highest rates reported were found for premenopausal, nulliparous women who smoked 20 cigarettes daily or more (OR = 7.08; 95% CI = 1.63–30.8) and had smoked for 20 cumulative pack-years or more (OR = 7.48; 95% CI = 1.59–35.2).²⁵⁴

Until recently, there was more evidence linking secondhand smoke than active smoking to breast cancer risk. Some current evidence suggests that both exposures increase breast cancer risk by about the same amount, even though passive smokers receive a much lower dose of carcinogens than do active smokers. In two studies examining effects of passive and active smoke exposures, duration of active smoking was associated with an increase in breast cancer risk, especially as number of cigarettes smoked increased.^{259,260} Similarly, exposure to passive smoke increased breast cancer incidence (OR = 2.3; 95% CI = 1.2–4.5²⁵⁹ and AOR = 3.21; 95% CI = 1.6–6.3²⁶⁰). Susceptibility to the effects of passive smoke may be influenced by race/ethnicity and genetic profiles: Hispanic and American Indian women

with a particular Interleukin 6 polymorphism (rs2069832 genotype) had an even higher risk (OR = 4.4; 95% CI = 1.5–12.8, *p* for interaction = 0.01) for premenopausal breast cancer.²⁵⁹

One possible explanation for the similar effects of active and passive smoke is that smoking acts as an anti-estrogen and damages the ovaries, thereby lowering estrogen levels. The lower level of estrogen may decrease breast cancer risk, while at the same time carcinogens in cigarette smoke increase a smoker's risk of breast cancer. Passive smokers, on the other hand, may not get a large enough dose of smoke to depress estrogen levels. A 2005 report from the Air Resources Board of California's Environmental Protection Agency concluded:

Overall, the weight of evidence (including biomarker, animal and epidemiological studies) is consistent with a causal association between environmental tobacco smoke (ETS) and breast cancer, which appears to be stronger for premenopausal women.²⁶¹

A recent review of the scientific literature confirmed the conclusion that where effects of environmental tobacco smoke on breast cancer risk are found, it is only significant for premenopausal women with the disease.²⁶²

Bisphenol A (BPA). BPA is one of the most commonly used chemicals. More than 2 billion pounds of BPA are produced in the United States each year, and several times that amount is produced globally.²⁶³ BPA is the building block of polycarbonate plastic and is also used in the manufacture of epoxy resins. Significant levels of BPA have been measured in ambient air²⁶⁴ and river and drinking water.²⁶⁵

BPA is commonly found in the lining of metal food cans and in some types of plastic food containers, including some baby bottles, water bottles, microwave ovenware and eating utensils. Because BPA is an unstable polymer and is also lipophilic, it can leach into infant formula and other food products, especially when heated.²⁶⁶ BPA can move into human tissue from ingested food products—a particular concern for women of childbearing age and young children. BPA has been found in blood samples from developing fetuses as well as in amniotic fluid,²⁶⁷ placental tissue, and umbilical cord blood at birth.²⁶⁸ CDC researchers found BPA in 95% of about 400 urine samples from a broad national sample of adults.⁹⁸

Several studies using both rat and mouse models have demonstrated that even brief exposures to environmentally relevant doses of BPA during gestation or around the time of birth lead to changes in mammary tissue structure predictive of later development of tumors. Exposure also increased sensitivity to estrogen at puberty.^{99,100,269,270} Recent data demonstrate that early exposure to BPA leads to abnormalities in mammary

tissue development that are observable even during gestation.¹⁰⁰ Prenatal exposure of rats to BPA also led to increases in the number of pre-cancerous lesions and in situ tumors (carcinomas¹⁰²), and an increased number of mammary tumors following adulthood exposures to a sub-threshold dose (lower than that needed to induce tumors) of a known carcinogen.²⁷¹

Studies using cultures of human breast cancer cells demonstrate that BPA acts through the same response pathways as natural estrogen (estradiol).^{272,273} BPA can interact weakly with the intracellular estrogen receptor, and it also can alter breast cell responsiveness and induce cell proliferation in vitro and in vivo. It affects cellular functions through interactions with the membrane estrogen receptor.^{274,275} Along with its many other effects on cell growth and proliferation, BPA has been shown to mimic estradiol in causing direct damage to the DNA of cultured human breast cancer cells.²⁷⁶

Alkylphenols. Alkylphenols are industrial chemicals used in the production of detergents and other cleaning products, and as anti-oxidants 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. In the Silent Spring Institute study of contaminants in samples from homes, alkylphenols—especially 4-nonylphenol (4-NP) and its breakdown products—were found in all samples of house air and 80% of house dust samples.⁶⁴ Substantial concentrations of these chemicals have also been found in wastewater associated with domestic and municipal landfills.²⁷⁷

The alkylphenols, including 4-NP, have been shown to mimic the actions of estradiol, mediating their effects through the cellular estrogen receptor.²⁷⁸ They also bind to the newly described cell membrane ER and mimic cellular signaling responses usually controlled by estradiol.²⁷⁹

Prenatal exposure of rats to 4-NP causes altered development of the mammary gland, as well as changes in steroid receptor populations in several reproductive tissues.²⁸⁰ Acevedo et al. found that treatment of mice with 4-NP led to an increased synthesis of estriol, a weak natural estrogen, by the livers of the treated animals. When compared with mice treated with equivalent amounts of estradiol, the mice exposed to 4-NP had an increased risk of mammary cancer.²⁸¹

Metals. Higher accumulations of iron, nickel, chromium, zinc, cadmium, mercury and lead have been found in cancerous breast biopsies as compared to biopsies taken from women without breast cancer. These metals also have been found in serum samples of women diagnosed with cancer as compared with healthy women.^{282,283} Laboratory studies have shown that a number of metals including copper, cobalt, nickel, lead, mercury, tin, cadmium and chromium have estrogenic effects on breast

cancer cells (MCF-7) cultured in vitro.^{284,285} Sukocheva et al. report that methyl mercury can significantly alter growth-related signaling in MCF-7 breast cancer cells—indicating that it, too, can disrupt the hormone-regulated cellular processes.²⁸⁶

Phthalates. Phthalates are a group of endocrine-disrupting chemicals commonly used to render plastics soft and flexible. They are found in soft plastic chew toys marketed for infants and in some varieties of nail polishes, perfumes, skin moisturizers, flavorings and solvents. Phthalates have been found in indoor air and dust,²⁸⁷ and in human urine and blood samples.²⁸⁸ Levels are highest in children ages 6–11 and in women.⁵¹

Phthalates are considered to be endocrine disruptors because of their complex effects on several hormonal systems including the estrogen and androgen hormone systems. The endocrine disrupting properties of this class of chemicals have been well established in the male offspring of female rats treated with phthalates while pregnant. Abnormalities reported included nipple retention, shortened ano-genital distance and increased cryptorchidism (undescended testes).^{289,290} Exposure of human mothers to phthalates, as measured by chemical analysis of urine samples, has also recently been associated with shortened ano-genital distances in newborn sons.²⁹¹

Some phthalates including butyl benzyl phthalate (BBP) and di-n-butyl phthalate (DBP) act as weak estrogens in cell culture systems. They can bind to estrogen receptors, induce estrogen-appropriate cellular responses and act additively with estradiol in altering these systems.^{292,293} BBP, DBP and another common phthalate, di-(2-ethylhexyl) phthalate (DEHP) significantly increase cell proliferation in MCF-7 breast cancer cells. In addition, these three phthalates inhibited the anti-tumor action of tamoxifen in MCF-7 breast cancer cells.²⁹⁴

In rat studies, phthalates have been shown to disrupt the development and functioning of male and female reproductive systems by interfering with the production of testosterone and estradiol, respectively.^{295,296} Phthalates also bind weakly to the androgen receptor, disrupting the cellular actions ordinarily initiated by the androgens.²⁹⁷ Those that bind most strongly to the androgen receptor, and therefore might be expected to exert the greatest effects through this pathway, include DBP, di-i-butyl phthalate (DIBP), and BBP.²⁹⁸ The role, if any, this androgenic pathway might play in breast cancer development remains to be explained.²⁹⁹

Parabens. Parabens are a group of compounds widely used as anti-microbial preservatives in food, pharmaceuticals, and cosmetics products, including underarm deodorants. Parabens are absorbed through intact skin and from the gastrointestinal tract and blood. Measurable concentrations of six different parabens have been

identified in biopsy samples from breast tumors.³⁰⁰ The particular parabens were found in relative concentrations that closely parallel their use in the synthesis of cosmetic products.³⁰¹ Parabens have also been found in almost all urine samples examined from a demographically diverse sample of U.S. adults.³⁰²

Parabens have been shown to be weak estrogen mimickers, binding to the cellular estrogen receptor.²⁶ They also increase the expression of genes that are usually regulated by estradiol and cause human breast tumor cells (MCF-7 cells) to grow and proliferate in vitro.³⁰³

Sunscreens (UV Filters). Growing concern about exposure to ultraviolet (UV) radiation from the sun and the risk of skin cancer has led to widespread use of sunscreens. Research has found that many sunscreens contain some chemicals (also used in various cosmetics) that are not only estrogenic but also lipophilic. Hayden et al. report that these chemicals are accumulating in wildlife and humans.³⁰⁴

In a study of six common sunscreen chemicals, Schlumpp et al. found five of them to exert significant estrogenic activity, as measured by the increase in proliferation rates of human breast cancer cells (MCF-7 cells) grown in vitro.³⁰⁵ These chemicals were 3-(4-methyl benzylidene)-camphor (4-MBC), octyl-methoxy-cinnamate (OMC), octyl-dimethyl-PABA (OD-PABA), bexophenone-3 (Bp-3) and homosalate (HMS). Hene-weer et al. found sunscreen chemicals OMC, 4-MBC, 2-hydroxy-4-methoxybenzophenone (BP-3) and its metabolite 2,4-dihydroxy-benzophenone (BP-1) to demonstrate estrogenic activation of pS2-gene transcription in MFC-7 cells. Mixtures of low concentrations of the four chemicals exerted an additive effect on gene transcription.³⁰⁶

Brand et al. found that application of OMC to the skin of the animals enhances the penetration of the endocrine-disrupting herbicide 2,4-D.³⁰⁷

Growth Promoters Used in Food Production (rBST and Zeranol)

Modern food-production methods have opened major avenues of exposure to environmental carcinogens and endocrine-disrupting compounds. Pesticides sprayed on crops, antibiotics used on poultry, and hormones injected into cattle, sheep and hogs involuntarily expose consumers to contaminants. Research suggests that some of these exposures may increase breast cancer risk.

Consumption of animal products also may pose risks because animal fat can retain pesticides, dioxins, and other environmental toxicants consumed by the animal. These lipophilic chemicals become more concentrated as they move from plants to animals and finally to humans.

The U.S. and Canadian beef, veal, and lamb industries have used synthetic growth hormones since the 1950s to hasten the fattening of animals. Several studies indicate that these growth enhancers may elevate the risk of breast cancer. Concerns about this and other health risks have led the European Union to ban imports of growth-hormone treated beef, including meat from the United States, since 1989.³⁰⁸

Bovine Growth Hormone (rBGH)/ Recombinant Bovine Somatotropin (rBST)

Despite opposition from individuals and groups concerned with both economic and health repercussions, the Food and Drug Administration in 1993 approved Monsanto's genetically engineered hormone product, recombinant bovine growth hormone (rBGH), for injection in dairy cows to increase milk production.³⁰⁹ This hormone quickly found its way (without labeling) into the U.S. milk supply, and from there into ice cream, buttermilk, cheese, yogurt and other dairy products. Since its introduction, rBGH (subsequently renamed recombinant bovine somatotrophin, rBST) has proven controversial because of its potential carcinogenic effects.

Although the data are complex, with some studies reaching different conclusions, several epidemiological studies have indicated a relationship between dairy consumption and breast cancer risk in pre-menopausal women (for a review of this research, see Outwater et al.³¹⁰). Drinking any type of cow's milk noticeably raises body levels of insulin growth factor 1 (IGF-1), a naturally occurring hormone in both cows and humans. Elevated levels of IGF-1 have been associated with increased risk of breast cancer.³¹¹ Injecting a cow with rBST stimulates additional production of IGF-1.³¹²

A prospective study of U.S. women found that pre-menopausal women with the highest levels of IGF-1 in their blood (drawn before cancer developed) were more likely to develop breast cancer as women with the lowest levels (OR = 1.6; 95% CI = 0.91–2.81). No increased risk was noted in post-menopausal women.³¹³ An association between circulating levels and IGF-1 and elevated risk of breast cancer has been found in pre-menopausal women in the U.K. (OR = 1.71; 95% CI = 0.74–3.95)³¹⁴ and U.S. (OR = 1.6; 95% CI = 1.0–2.6).³¹⁵ These studies confirm earlier research linking elevated levels of IGF-1 with increased breast cancer risk.^{316–318}

Laboratory studies have shown that IGF-1 can regulate the growth and increase the proliferation of breast cancer cells (MCF-7) grown in vitro³¹⁹ and decrease the death of mammary tumor cells in laboratory animals.³²⁰

Proponents of rBST argue that IGF-1 is harmless because it occurs naturally in humans, is contained in human saliva and is broken down during digestion. However, animal evidence indicates that digestion does not break down IGF-1 in milk because casein, the prin-

cipal protein in cow's milk, protects IGF-1 from the action of digestive enzymes.³²¹

Zeranol (Ralgro). One of the most widely used chemicals in the U.S. beef industry is zeranol (Ralgro). Zeranol is a potent nonsteroidal growth promoter that mimics many of the effects of the natural hormone estradiol. Leffers et al. compared the potency of zeranol to other endocrine disruptors and concluded, "The very high potency of zeranol . . . suggests that zeranol intake from beef products could have greater impact on consumers than the amounts of [other] known or suspected endocrine disruptors that have been found in food."³²²

A series of studies examined estrogenic activity in normal breast epithelial cells and breast cancer cells. Abnormal cell growth was significant even at zeranol levels almost 30 times lower than the FDA-established limit in beef.³²³ Follow-up work demonstrated that zeranol is comparable to natural estrogen (estradiol) and the synthetic estrogen diethylstilbestrol (DES) in its ability to transform MCF-10A human breast epithelial cells to a pre-cancerous profile in vitro.³²⁴

Evidence Linking Other Chemicals of Concern to Breast Cancer

Benzene

Benzene is one of the highest volume petrochemical solvents currently in production, and global production rates are expected to continue to grow over the next several years. Chemical industries estimate that more than 42 million metric tons (more than 105 billion pounds) of benzene will be produced globally by the year 2010.³²⁵ Exposures to benzene come from inhaling gasoline fumes, automobile exhaust, cigarette smoke (primary and secondary), and from industrial burning. Benzene presents a serious occupational hazard for people exposed through their work in chemical, rubber and shoe manufacturing, and oil and gasoline refining industries. Both the NTP and IARC have designated benzene as a known human carcinogen.^{326,327}

Epidemiological studies of the effects of benzene on breast cancer risk are difficult to conduct, mainly because exposures to benzene occur in conjunction with exposures to other chemicals that are also released in combustion and manufacturing processes. Also, few of the occupational studies focusing on chemical and automotive industries have included women in substantial numbers to draw meaningful conclusions. Petralia et al. found that among female workers in China, benzene exposure was associated with an elevated risk of breast cancer. They found elevated risk for breast cancer in scientific research workers, medical and public health workers, electrical and electronic engineers, teachers, librarians and accountants.³²⁸ Results from recent studies examining occupational

exposures among enlisted women in the U.S. Army³²⁹ and women in various professions in Israel³³⁰ support these conclusions.

Hansen looked at breast cancer in men with exposure to benzene and associated chemicals, and found that men with occupational exposures to gasoline fumes and combustion had significantly increased rates of breast cancer.¹²⁷ The effect was most pronounced among men who started at their jobs before the age of 40.

Benzene administration to laboratory mice induces mammary tumors.³³¹ One study found that mice exposed to benzene have frequent mutations of genes that are responsible for suppressing the development of tumors.³³²

Organic Solvents Other than Benzene

Industrial use of organic solvents has increased over the last several decades, particularly in the manufacture of computer components. Some solvents used in this industry (including toluene, methylene chloride and trichloroethylene) have been shown to cause mammary tumors in laboratory animals.³³³ Such solvents are also used in other industries, such as manufacturing of cleaning products and cosmetics.³³⁴

Organic solvents are lipophilic and accumulate in the fat tissue of the breast. They are also passed from mother to infant through breast feeding.³³⁵

Several epidemiological studies have linked occupational exposures to organic solvents with increases in breast cancer incidence. Two recent studies showed an increased risk of breast cancer among workers exposed to chlorinated organic solvents in semiconductor plants.^{336,337} A Danish study showed that women ages 20–55 employed in solvent-using industries (fabricated metal, lumber, furniture, printing, chemical, textile and clothing industries) for >10 years had double the risk of breast cancer compared to women employed outside these industries (OR = 1.97; 95% CI = 1.39–2.79).³³⁸ A 1995 U.S. study suggested an increased breast cancer risk associated with occupational exposure to styrene, as well as with several other organic solvents including carbon tetrachloride and formaldehyde.³³⁹ These results were validated by studies in Finland, Sweden and Italy.^{340–343}

Mixtures of organic solvents, similar to what might be seen in an industrial setting, induced dose-dependent increases in mammary tumors when young (pre-pubertal) laboratory mice were exposed to the chemicals.³⁴⁴ Laboratory studies have shown that some organic solvents are mutagens and carcinogens.³³³

Vinyl Chloride

Manufacturers use polyvinyl chloride (PVC) extensively to produce food packaging, medical products, appliances, cars, toys, credit cards and rainwear. When PVC

is made, vinyl chloride monomer may be released into the air or wastewater. Vinyl chloride has also been found in the air near hazardous waste sites and landfills and in tobacco smoke.

Vinyl chloride was one of the first chemicals designated as a known human carcinogen by the National Toxicology Program (NTP)³⁴⁵ and IARC.³⁴⁶ Vinyl chloride has also been linked to increased mortality from breast and liver cancer among workers involved in its manufacture.^{347,348} Animals exposed long-term to low levels of airborne vinyl chloride show an increased risk of mammary tumors.³⁴⁹

1, 3-Butadiene

1,3-butadiene is an air pollutant created by internal combustion engines and petroleum refineries. It is also a chemical used in the manufacture and processing of synthetic rubber products and some fungicides. In addition, 1,3-butadiene is found in tobacco smoke.

The EPA determined that 1,3-butadiene is carcinogenic to humans, with the main route of exposure being inhalation.³⁵⁰ The National Toxicology Program classifies 1,3-butadiene as a known human carcinogen.³⁵¹ Data from research on animals indicate that females may be more vulnerable to the carcinogenic effects of 1,3-butadiene,³⁵⁰ which is known to cause mammary and ovary tumors in female mice and rats. This pollutant produces even greater toxic effects in younger rodent populations.^{352,353}

Ethylene Oxide

Ethylene oxide is a fumigant used to sterilize surgical instruments and is also used in some cosmetics products.³⁵⁴ Ethylene oxide is classified as a known human carcinogen and is one of 48 chemicals that the National Toxicology Program identifies as mammary carcinogens in animals.³⁵⁵

Steenland et al. looked at breast cancer incidence in 7,576 women exposed to ethylene oxide while working in commercial sterilization facilities. They found an increased incidence of breast cancer among these women in direct proportion to their cumulative exposure to ethylene oxide.³⁵⁶ Although there are contradictory data in the recent literature, several other reports support the finding that exposure to ethylene oxide is associated with increased risk for breast cancer in women.³⁵⁷

Studies in which human breast cells grown in vitro were exposed to low doses of ethylene oxide demonstrated that the chemical exposure resulted in a significant increase in damage to the cells' DNA.³⁵⁷

Aromatic Amines

Aromatic amines are a class of chemicals found in the plastic and chemical industries, as byproducts of the

manufacturing of compounds such as polyurethane foams, dyes, pesticides, pharmaceuticals and semiconductors.³⁵⁸ They are also found in environmental pollution, such as diesel exhaust, combustion of wood chips and rubber, and tobacco smoke, and in grilled meats and fish.³⁵⁹ There are three types of aromatic amines: monocyclic, polycyclic and heterocyclic.

Three monocyclic amines, including o-toluidine, have been identified in the breast milk of healthy lactating women.³⁵⁸ O-Toluidine is known to cause mammary tumors in rodents.^{360,361} These data demonstrate that the mother's mammary tissue and the nursing child are exposed to environmental carcinogens during breastfeeding.

Heterocyclic aromatic amines (HAAs) are formed, along with PAHs, when meats or fish are grilled or otherwise cooked at high temperatures. Steck et al. found an association between higher lifetime consumption of grilled meats and fish and increased incidence of postmenopausal breast cancer.³⁶² Studies of both milk and cells from the ducts of women's breast revealed the presence of DNA adducts in association with HAAs.^{363,364} These DNA adducts are indicators of problems in DNA repair in cells, one of the early hallmarks of tumor development.

Laboratory studies of HAAs in systems using cultured breast cancer cells demonstrate that these chemicals can mimic estrogen, and they also can have direct effects on cell division processes in ways that, if also found in in vivo studies with intact tissues, might enhance the development of tumors.³⁶⁵

Evidence Linking Radiation to Breast Cancer

Ionizing Radiation

Ionizing radiation is any form of radiation with enough energy to break off electrons from atoms. This radiation can break the chemical bonds in molecules, including DNA molecules, thereby disturbing their normal functioning. X-rays and gamma rays are the only major forms of radiation with sufficient energy to penetrate and damage body tissue below the surface of the skin.

Among the many sources of ionizing radiation are traditional X-rays, computed tomography (CT) scans, fluoroscopy and other medical radiological procedures. Sources of gamma rays include emissions from nuclear power plants, scientific research involving radionuclides, military weapons testing and nuclear medicine procedures such as bone, thyroid and lung scans.³⁶⁶

In 2005, the National Toxicology Program classified X-radiation and gamma radiation as known human carcinogens.³⁶⁷ No safe dose of radiation has been identified.³⁶⁸⁻³⁷² Radiation damage to genes is cumulative over a lifetime.¹⁰⁸ Repeated low-dose exposures over time may have the same harmful effects as a single high-dose exposure.

Exposure to ionizing radiation is the best- and longest-established environmental cause of human breast cancer in both women and men. Ionizing radiation can increase the risk for breast cancer through a number of different mechanisms, including direct mutagenesis, genomic instability,^{373,374,374} and changes in breast cell micro-environments that can lead to damaged regulation of cell-cell interactions within the breast.^{376,377} Ionizing radiation not only affects cells that are directly exposed, but it can also alter the DNA, cell growth and cell-cell interactions of neighboring cells, referred to as the "bystander effect."^{378,379}

Interactions Between Radiation and Other Factors. There are a number of factors that may interact with radiation to increase the potency of its carcinogenic effect. Some of these factors include a woman's age at exposure, genetic profile and possibly estrogen levels. It has been well established in a number of studies of women exposed to military, accidental or medical sources of radiation that children and adolescents who are exposed are more seriously affected in their later risk for breast cancer than are older women.¹⁰⁸ In addition, recent genetic data indicate that women with some gene mutations (e.g., ATM, TP53 and BRCA1/2) are more likely to develop breast cancer and may be especially susceptible to the cancer-inducing effects of exposures to ionizing radiation.^{380,381}

Studies using animal and in vitro human breast tumor cell culture models have demonstrated that the effects of radiation on mammary carcinogenesis may be additive with effects of estrogens.³⁸²⁻³⁸⁴ This is of particular concern given the widespread exposure to estrogen-mimicking chemicals in our environment and the multiple sources of ionizing radiation.

Evidence Linking Ionizing Radiation and Breast Cancer Risk. The link between radiation exposure and breast cancer has been demonstrated in atomic bomb survivors.^{110,111} Rates of breast cancer were highest among women who were younger than age 20 when the United States dropped atomic bombs on Hiroshima and Nagasaki.³⁸⁵ In addition, Ron et al. reported a significant association between ionizing radiation exposure and the incidence of male breast cancer in Japanese atomic bomb survivors.³⁸⁶

Use of X-rays to examine the spine, heart, lungs, ribs, shoulders and esophagus also exposes parts of the breast to radiation. X-rays and fluoroscopy of infants irradiate the whole body.³⁸⁷ Decades of research have confirmed the link between radiation and breast cancer in women who were irradiated for many different medical conditions, including tuberculosis,³⁸⁸ benign breast disease,³⁸⁹ acute postpartum mastitis,³⁹⁰ enlarged thymus,¹¹⁷ skin hemangiomas,³⁹¹ scoliosis,¹¹³ Hodgkin's disease,³⁹⁰⁻³⁹⁹ non-Hodgkin's lymphoma,¹¹⁵ and even treatment for acne⁴⁰⁰ and prophylactic dental

care.¹¹⁸ Again, evidence from almost all conditions suggests that exposure to ionizing radiation during childhood and adolescence is particularly dangerous with respect to increased risk for breast cancer later in life.

A recent study of female radiology technologists who had sustained daily exposures to ionizing radiation demonstrated an increased risk of breast cancer for those women who began working during their teens or, independent of age, working in the field before the 1940s, when exposure levels were substantially higher than they have been in more recent decades.^{401,402} And a recent review and analysis of all existing related studies found that women who work as airline flight attendants had increased levels of breast cancer. Factors that could explain this increase may include lifestyle and reproductive histories, as well as increased exposures to cosmic (atmospheric) ionizing radiation.⁴⁰³

Medical Radiation: Risks and Benefits. There is credible evidence that medical X-rays (including mammography, fluoroscopy and CT scans) are an important and controllable cause of breast cancer.^{404,405} Although X-rays have been a valuable diagnostic tool for more than a century, the radiation dose has not always been carefully controlled.⁴⁰⁶ However, the dose given per X-ray has been drastically reduced over the past several decades and the regulatory oversight of equipment and personnel has increased. In mammography, for example, efforts to reduce the radiation dose to as low as reasonably achievable (ALARA) levels have lowered the radiation dose from an estimated 2 rads in 1976 to 0.2 rads today, without compromising image quality.⁴⁰⁵ Nevertheless, a recent study has indicated that exposure of women to multiple screening mammograms beginning before the age of 35 was associated with an increased presentation of breast cancer before the age of 50 years.¹¹⁸

Although there has been a significant decrease in exposures to ionizing radiation from individual X-rays, the introduction of CT scans in the 1970s greatly increased the radiation dose per medical examination. According to the National Cancer Institute, CT scans “comprise about 10% of diagnostic radiological procedures in large U.S. hospitals,” but contribute an estimated 65% of the effective radiation dose to the public from all medical X-ray examinations.⁴⁰⁷

Some studies suggest that doctors and patients should carefully evaluate the risks and benefits of radiation therapy for survivors of early breast cancer, particularly older women. Women older than age 55 derive less benefit from radiation therapy as measured by a reduced rates of local recurrence of cancer⁴⁰⁸ and may face increased risks of radiation-induced cardiovascular complications,⁴⁰⁹ as well as secondary cancers such as leukemias and cancers of the lung, esophagus, stomach and breast.^{410,411} Using SEER data from the National

Cancer Institute, Huang and Mackillop showed a 16-fold increase in relative risk of angiosarcoma of the breast and chest wall following irradiation to a primary breast cancer.⁴¹²

Non-ionizing Radiation (Electromagnetic Fields)

Electromagnetic waves are a type of non-ionizing radiation, i.e., a type of low-frequency radiation without enough energy to break off electrons from their orbits around atoms and ionize the atoms. Microwaves, radio waves, radar and radiation produced by electrical transmission are examples of radiation sources that generate electromagnetic fields (EMF). Electric lighting also generates EMF. Fluorescent lighting and many types of low-voltage lighting produce fields that are particularly high compared to incandescent lighting. In addition, computers and many other types of wired and wireless electronic equipment (e.g., cell phones) all create EMF of varying strengths.

IARC has classified EMF as possible human carcinogens based on the scientific literature related to EMF and childhood leukemias.⁴¹³ In 1998, a National Institute of Environmental Health Sciences (NIEHS) EMF Working Group recommended that low-frequency EMF, such as those from power lines and electrical appliances, be classified as possible human carcinogens, again primarily based on evidence related to childhood leukemias.⁴¹⁴ However, consensus has been more difficult to reach about the relationship between EMF and breast cancer.

Exposure levels of EMF have increased exponentially in the past two decades due to the widespread use and deployment of wired and wireless technologies, including city-wide Wi-Fi networks in the U.S. and Europe. Everyone in industrialized countries is exposed to EMF from multiple sources every day, and many of these exposures are involuntary.

Despite rising exposure levels, over the past decade there has been little federally funded research in the U.S. on the possible health effects of EMF. However, Research has continued internationally. In August 2007, an international team of researchers released a summary analysis of the science on EMF and potential health concerns, including breast cancer and other cancers as well as neurodegenerative diseases and disorders. Based on a review of more than 2,000 studies, and endorsed by the European Environmental Agency, it calls for stronger safety standards on EMF exposure to prevent future cancers and other diseases and disorders.⁴¹⁵

Not all epidemiological or occupational studies have found significant relationships between exposures to EMF and risk for breast cancer.⁴¹⁶ However, a recent population-based case-control study in the United States by McElroy et al. looked at breast cancer risk in women who were exposed occupationally to low, medium or high levels of EMF in their respective work environments.

Although the increases in incidence were low as EMF exposures increased, they were sufficiently robust to lead the authors to conclude that their results, "taken together with previous epidemiological studies, suggest that exposure to EMF in the workplace may be associated with a slight elevation in breast cancer risk."⁴¹⁷

Recently, a second very large population-based, case-control study from Poland found an increased risk for breast cancer in women working in white-collar jobs such as marketing, advertising, management, engineering (electrical, computer, industrial, etc.), social science and economics. Peplonska et al. found increased risk of breast cancer in blue collar jobs including machine operators in a variety of settings. No single chemical or other exposure can be linked to the occupations with excess risk, leading the authors to conclude that possible associations of these occupations with EMF deserve further attention.⁴¹⁸

Kliukiene et al. reported an increased risk of breast cancer among Norwegian female radio and telegraph operators exposed to radiofrequency (one type of EMF) and extremely low frequency EMF. Pre-menopausal women showed an increased risk of estrogen-receptor-positive tumors (OR = 1.78; 95% CI = 0.59–5.41) and post-menopausal women had an increased risk of estrogen-receptor-negative tumors (OR = 2.37; 95% CI = 0.88–6.36).⁴¹⁹

Other research on EMF exposure has shown increased mortality from breast cancer in women employed in the telephone industry (MOR = 1.6).⁴²⁰ Pre-menopausal women appear to be at higher risk (OR = 1.98) than are post-menopausal women (OR = 1.33).⁴²¹

In 2004, a Norwegian study of residential and occupational EMF exposure found a 60% increase in breast cancer risk among Norwegian women of all ages living near high-voltage power lines. Occupational exposure also increased risk, but not as much as residential exposure. Women younger than age 50 who were exposed to EMF both at home and at work showed an increase in risk of breast cancer (OR = 1.58; 95% CI = 1.30–1.92).⁴²² A Swedish study found that for women under the age of 50, residential exposure to EMF was associated with a significant increase in incidence of ER+ breast tumors (OR = 7.4; 95% CI = 1.0–178.1).⁴²³

A 2003 study suggested that EMF exposure from electric bedding (electric blankets, mattress pads and heated waterbeds) may increase the risk of breast cancer in African American women (OR = 1.9; 95% CI = 1.0–3.7).⁴²⁴ Researchers from Walter Reed Army Medical Center and Meharry Medical College compared 304 African American women with breast cancer to 305 African American women who did not have the disease. They found that the longer a woman used an electric bedding device, the greater her risk of breast cancer. Most earlier studies on electric bedding use among Caucasian women did not show an association with increased breast cancer risk.

Although breast cancer is rare in men, numerous studies point to a connection between EMF exposure and male breast cancer.^{133,416,425–428}

EMF can also cause increases in mammary tumors in laboratory animals and in vitro systems in which human breast cell tumors are grown in culture. These live animal effects are found in some strains of animals but not others, indicating that subtle differences in genetic background might make some animals more susceptible to the carcinogenic effects of EMF.⁴²⁹

The mechanisms by which EMF can affect health are not completely understood. The most widely studied model is built on the finding that EMF exposure and increased light at night lower the body's level of melatonin, a hormone secreted by the pineal gland during darkness.⁴³⁰ Through complex interactions with estrogens and cell signaling pathways,⁴³¹ melatonin appears to have anti-cancer properties.⁴³² In a variety of laboratory animal and in vitro systems, melatonin has inhibited the growth of mammary tumor cells.⁴³³

Research has shown that exposure to light at night also decreases melatonin levels. This finding led to the hypothesis that night-shift work (working at night in a lighted environment) may increase the risk of breast cancer by lowering melatonin levels. Although this hypothesis remains controversial, at least three studies suggest a link between night-shift work and increased risk of breast cancer.^{434–436} In recent prospective studies, higher melatonin levels were associated with a lower risk of breast cancer in both premenopausal (OR = 0.70; 95% CI = 0.47–1.06)⁴³⁷ and postmenopausal (OR = 0.56; 95% CI = 0.33–0.97)⁴³⁸ women.

CONCLUSIONS

We have provided evidence that exposures to a wide variety of environmental chemicals and radiation, alone and in combination with other environmental factors, genetic profiles and other more commonly addressed risk factors for breast cancer, together are implicated in the high incidence of breast cancer observed over the second half of the 20th century and into the 21st. We also report on the growing evidence from both human and animal studies that prenatal exposures to toxicants, or exposures during early childhood through adolescence, can have profound and long-term effects on risk for developing breast cancer later in life.

Although the evidence we have presented is clearly compelling in making the links between numerous environmental factors and breast cancer, considerable work remains to be done in order to better understand the complexity of these links and their multiple interactions. We need more and better data on human populations, using both occupational studies in which fewer people are exposed to higher doses of contaminants and broader environmental studies of larger

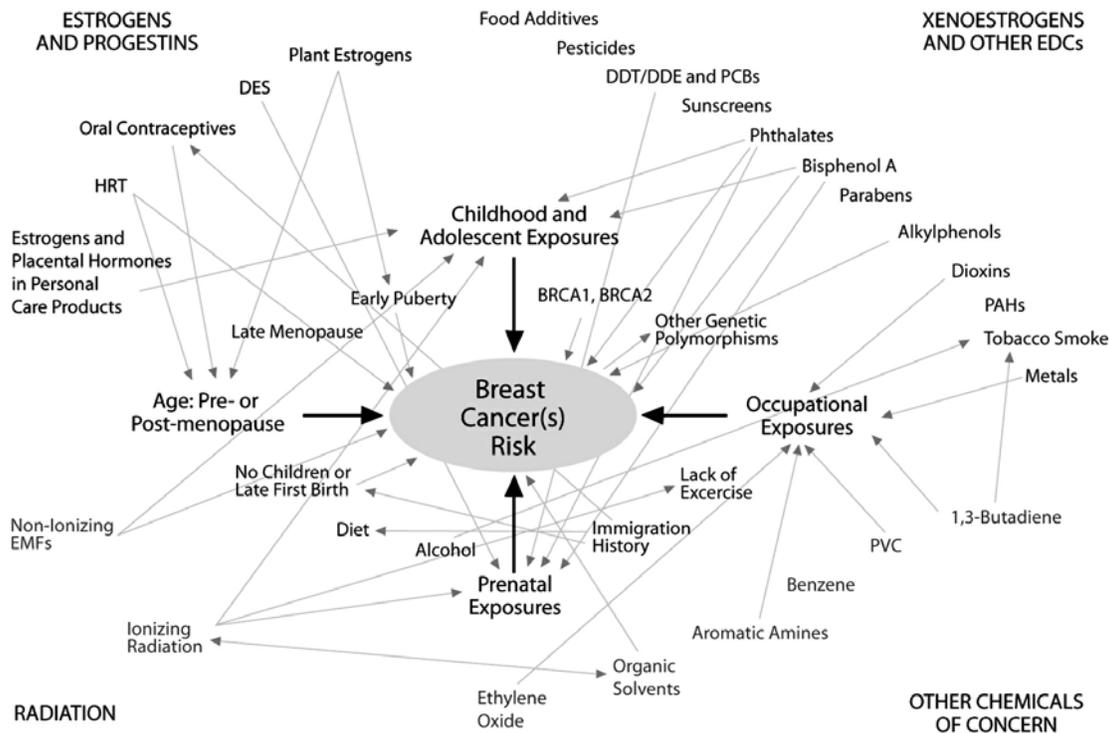


Figure 1—Complexity of Breast Cancer Causation

numbers of people exposed to lower doses of contaminants in their daily lives. Where possible, epidemiological studies need to focus on mixtures of exposures—including low dose exposures—at critical times during development, from the prenatal period through childhood and adolescence, pregnancy and lactation, and ultimately menopause. Difficult-to-conduct human studies must be supplemented by parallel studies using relevant animal and in vitro models, enhancing the power of our understanding of potential mechanisms underlying the links between environmental factors and breast disease. As we move forward in developing research strategies and designs, we argue for the need to take a complex view of the interactive actions between various risk factors for disease, including environmental, reproductive, genetic and epigenetic, and lifestyle factors. This will require moving away from studies that examine or conceptualize risk factors as working in isolation and move towards an understanding of those risks in a more complex, web-like framework of often interconnected factors, each exerting direct and interactive effects on cellular processes in mammary tissue (see Fig. 1).

This scientific evidence presented in this report also supports a call for action at the local, state and federal levels to identify and eliminate environmental causes of the disease. Toward this end, the companion article⁴³⁹ to this scientific review provides state and federal policy recommendations, as well as research recommendations, for addressing these critical issues.

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APPENDICES

APPENDIX 1

*Chemicals Shown to Cause Mammary Gland Tumors in Animal Studies*⁶⁵

Key:

IARC (International Agency for Research on Cancer) carcinogenic risk classification, based on evaluation of potential tumor development at all sites, not only breast/mammary tissue: Group 1 – This chemical is carcinogenic to humans; Group 2A - This chemical is probably carcinogenic to humans; Group 2B – This agent is possibly carcinogenic to humans.¹

MamList: Identifies the source from which scientists at the Silent Spring Institute have identified the chemical as causing mammary tumors in animal models: **P**—Carcinogenicity Potency Database;² **I**—IARC Monographs;³ **N**—National Toxicology Program technical reports or the 11th Report on Carcinogens (NTP 2002);^{4,5} **C**—National Library of Medicine Chemical Carcinogen Research Information System.⁶

IARC	MamList	Chemical	Category
1	P,N,C	benzene	Industrial Chemical
1	P,I,N	ethylene oxide	Industrial Chemical
1	P,I,N,C	vinyl chloride (PVC)	Industrial Chemical
1	P,I,N,C	4-aminobiphenyl	Dye
1	P,I,N	benzidine	Dye
1	P,C	chloroambucil	Pharmaceutical
1	N,C	cyclophosphamide	Pharmaceutical
1	I,N,C	thiotepa	Pharmaceutical
1	P,I,N,C	diethylstilbestrol	Hormone
1	I,C	estrogens, steroidal	Hormone
1	I,C	estrogens, nonsteroidal	Hormone
1	I,C	estrogen therapy, postmenopausal	Hormone
1	I,C	estrogen-progestogen menopausal therapy	Hormone
1	I,C	estrogen-progestogen oral contraceptives	Hormone
1	I,N	wood dust	Natural Product
2A	P,I,N,C	ethylene dibromide (1,2-dibromoethane)	Industrial Chemical
2A	P,N,C	1,3-butadiene	Industrial Chemical
2A	P,I,N,C	4,4'-methylene-bis(2-chloroaniline)	Industrial Chemical
2A	P,I,N,C	acrylamide	Industrial Chemical
2A	P,I,N,C	glycidol	Industrial Chemical
2A	I,N	indium phosphide	Industrial Chemical
2A	P,I,N	ortho-toluidine	Industrial Chemical
2A	P,I,N,C	vinyl fluoride	Industrial Chemical
2A	P,I,N,C	1,2,3-trichloropropane	Chlorinated Solvent
2A	N,C	benzo[a]pyrene	Product of Combustion
2A	N	dibenz[a,h]anthracene	Product of Combustion
2A	P,I,N,C	IQ	Product of Combustion
2A	P	chlordane	Pesticide
2A	P,I,N,C	benzidine base dyes: Direct Black 38	Dye
2A	P	azacitidine	Pharmaceutical
2A	I,N,C	adriamycin	Pharmaceutical
2A	P	phenacetin	Pharmaceutical
2A	P,I,N,C	procarbazine hydrochloride	Pharmaceutical
2A	I,N	androgenic (anabolic) steroids	Hormone
2A	N,C	n-nitroso-n-methylurea	Research Chemical

IARC	MamList	Chemical	Category
2B	P,I	1,2-propylene oxide	Industrial Chemical
2B	P,I,C	1,4-dioxane	Industrial Chemical
2B	P,I,N,C	2,2-bis(bromomethyl)propane-1,3-diol	Industrial Chemical
2B	I,N,C	2,3-dibromopropan-1-ol	Industrial Chemical
2B	P,N,C	2,4-diaminotoluene	Industrial Chemical
2B	P,I,N,C	2,4-dinitrotoluene	Industrial Chemical
2B	N,C	2-methylaziridine	Industrial Chemical
2B	P,I,N,C	5-nitroacenaphthene	Industrial Chemical
2B	P,I,N,C	acrylonitrile	Industrial Chemical
2B	P,I,C	AF-2(2-furyl)-3-(5-nitro-2-furyl) acrylamide	Industrial Chemical
2B	P,I,N,C	chloroprene	Industrial Chemical
2B	I	hydrazine	Industrial Chemical
2B	P,N,C	nitrobenzene	Industrial Chemical
2B	P,I,N,C	nitromethane	Industrial Chemical
2B	N	n-nitroso-di-n-butylamine	Industrial Chemical
2B	N	ortho-aminoazotoluene	Industrial Chemical
2B	P,I,N,C	1,3-propane sultone	Industrial Chemical
2B	P,I,C	styrene	Industrial Chemical
2B	N,C	ethyl carbamate (urethane)	Industrial Chemical
2B	P,I,N,C	1,2-dichloroethane	Chlorinated Solvent
2B	P,I,N	carbon tetrachloride	Chlorinated Solvent
2B	P,I,N,C	dichloromethane (methylene chloride)	Chlorinated Solvent
2B	I,N,C	1,8-dinitropyrene	Product of Combustion
2B	P,I,N,C	1-nitropyrene	Product of Combustion
2B	I	2-nitrofluorene	Product of Combustion
2B	C	Trp-P-2 (3-amino-1-methyl-5h-pyrido[4,3-b]indole)	Product of Combustion
2B	I,N,C	4-nitropyrene	Product of Combustion
2B	N	6-nitrochrysene	Product of Combustion
2B	C	dibenzo[a,e]pyrene (dibenzo[def,p]chrysene)	Product of Combustion
2B	I,N,C	isoprene	Product of Combustion
2B	I,N,C	MeIQ (2-amino-3,4-dimethylimidazo[4,5-f]-quinoline)	Product of Combustion
2B	I,N,C	PhIP (2-amino-1-methyl-6-phenylimidazo[4,5-b]-pyridine)	Product of Combustion
2B	P	chlordane	Pesticide
2B	P,I,N,C	1,2-dibromo-3-chloropropane	Pesticide
2B	N,C	dichlorvos	Pesticide
2B	P,I,C	2-(2-formylhydrazino)-4-(5-nitro-2-furyl)thiazole (nifurthiazole)	Pesticide
2B	P,I,N,C	sulfallate	Pesticide
2B	P,I,N,C	3,3'-dichlorobenzidine	Dye
2B	N	3,3'-dimethoxybenzidine	Dye
2B	N	3,3'-dimethylbenzidine	Dye
2B	P,I	4,4'-methylene-bis(2-methylaniline)	Dye
2B	N	C.I. Acid Red 114	Dye
2B	N,C	C.I. Basic Red 9	Dye
2B	P,I,C	FD & C Violet No. 1	Dye
2B	I,C	n,n'-diacetylbenzidine	Dye
2B	P,I,C	3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX)	Drinking Water Disinfectant
2B	P,I,C	1-[(5-nitrofurfurylidene)amino]-2-imidazolidinone	Pharmaceutical
2B	P,I,C	2-amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	Pharmaceutical
2B	I	5-morpholinomethyl-3-[(nitrofurfurylidene)amino]-2-oxazolidinone	Pharmaceutical
2B	I	amsacrine	Pharmaceutical
2B	P,I,N	dacarbazine	Pharmaceutical
2B	I,C	daunomycin	Pharmaceutical
2B	P	griseofulvin	Pharmaceutical
2B	I,C	merphalan	Pharmaceutical
2B	P,I,N,C	metronidazole	Pharmaceutical
2B	C	mitomycin-c	Pharmaceutical
2B	P,I,C	<i>n</i> -[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide	Pharmaceutical
2B	I,C	niridazole	Pharmaceutical
2B	I	trans-2-[(dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)-vinyl]-1,3,4-oxadiazole	Pharmaceutical
2B	I,C	uracil mustard	Pharmaceutical
2B	P,N,C	ochratoxin A	Natural Product
2B	N	ethyl methanesulfonate	Research Chemical

APPENDIX 2

List of Endocrine Disrupting Compounds

Compound	Exposures/Uses
Pesticides	
Atrazine	Selective herbicide
Chlordane	Insecticide (ticks and mites), veterinary pharmaceutical
Chlorpyrifos	Insecticide (ticks and mites)
Cypermethrin	Insecticide
2,4-Dichlorophenoxyacetic acid	Herbicide
DDT (and associated compounds)	Contact insecticide
Dieldrin, aldrin, endrin	Insecticide
Lindane	Insecticide
Malathion	Insecticide
Methoxychlor	Insecticide, veterinary pharmaceutical
Pentachlorophenol	Insecticide (termites), wood preservative
Permethrin, sumithrin	Insecticide
Toxaphene	Insecticide
Tributyl tin (chloride)	Biocide, rodent repellent
Vinclozolin	Agricultural fungicide
Persistent non-pesticide organochlorines and PAHs	
PAHs	Compounds in industrial air pollutants, smoke from cola or coke-burners, tobacco tar, some foods
Polybrominated biphenyls	Flame retardant
Polybrominated diphenyl ethers	Flame retardant
PCBs (Aroclor 1254)	Production of electrical capacitors and transformers and other electrical equipment; carbonless copy paper
Dioxins and furans	Byproduct of incineration, paper manufacturing, production of chlorine aromatics; impurity in some herbicides
Phenols and alkylphenols	
Bisphenol A	Polycarbonate and polyester-styrene resins
4-tert-Butylphenol	Intermediate in manufacturing of varnish and lacquer resins, soap antioxidant
Nonylphenol polyethoxylate, 4-nonylphenol, 4-octylphenol	Surfactant, detergent, defoaming agent, some pesticides, degradation product of alkylphenol, ethoxylated antioxidant in some plastics
o-Phenylphenol	Disinfectant fungicide, rubber production
Phthalates	
bis(2-Ethylhexyl) phthalate, butyl benzyl phthalate	Plasticizer for polyvinyl chloride (PVC) polymers
Di-n-butyl phthalate, diethyl phthalate inks, adhesives	Personal care products including nail polish, perfume, hair spray; plasticizers,
Parabens	
Butyl-, ethyl-, methyl-, and propyl- parabens	Pharmaceutical antifungal agent, preservative in foods, antimicrobial in creams, lotions, ointments and other cosmetics
Other Organics	
Amsonic acid	Used in manufacturing of dyes, bleaching agents, optical brighteners, whitening agents
Styrene	Used in manufacturing of plastics, synthetic rubber, resins; insulator
Vinyl acetate	Used in production of wide range of polymers, paints, food packaging
Metals	
Cadmium, lead	Batteries, plastic stabilizers, pigments
Mercury	Thermometers, dentistry, pharmaceuticals, anti-fouling paints
Phytoestrogens	
Genestein, coumestrol, zearalenone	Soy, grains, grain molds