Environmental Pollutants and Breast Cancer

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Breast cancer is the most common cancer in women and the leading cause of cancer death among women 35–54 years of age. Rising incidence, increased risk among migrants to higher risk regions, and poor prediction of individual risk have prompted a search for additional modifiable factors. Risk factors for breast cancer include reproductive characteristics associated with estrogen and other hormones, pharmaceutical hormones, and activities such as alcohol use and lack of exercise that affect hormone levels. As a result, investigation of hormonally active compounds in commercial products and pollution is a priority. Compounds that cause mammary tumors in animals are additional priorities. Animal models provide insight into possible mechanisms for effects of environmental pollutants on breast cancer and identify chemical exposures to target in epidemiologic studies. Although few epidemiologic studies have been conducted for chemical exposures, occupational studies show associations between breast cancer and exposure to certain organic solvents and polycyclic aromatic hydrocarbons (PAHs). Population-based studies have been limited to a few organochlorine compounds and PAHs and have been mostly negative. A variety of challenges in studies of breast cancer and the environment may have contributed to negative findings. Lack of exposure assessment tools and few hypothesis-generating toxicologic studies limit the scope of epidemiologic studies. Issues of timing with respect to latency and periods of breast vulnerability, and individual differences in susceptibility pose other challenges. Substantial work is needed in exposure assessment, toxicology, and susceptibility before we can expect a pay-off from large epidemiologic studies of breast cancer and environment. *Key words:* **benzene, breast cancer, carcinogens, endocrine-disrupting compounds, estrogen, hormonally active agents, organic solvents, PAHs, pesticides.** *Environ Health Perspect* **111:1007–1019 (2003). doi:10.1289/ehp.6310 available via** *http://dx.doi.org/* **[Online 19 May 2003]**

Breast cancer is the most common cancer in women (Parkin et al. 2001). Incidence is highest in North America, Northern Europe, and Australia, where age-adjusted rates are 75–92 per 100,000 women (standardized to year 2000 world population), and lowest in Asia and Africa, where incidence is less than 22 per 100,000 (Parkin et al. 2001). Mortality has increased steadily from the 1960s until the late 1980s, when rates declined in many countries, including the United States (Parkin et al. 2001). Mortality continued to climb, however, for African Americans, whose mortality rates have exceeded the U.S. average since the 1980s (SEER 2002). Worldwide, breast cancer incidence continues to rise in all age groups, with an increase in U.S. age-adjusted incidence of more than 40% from the early 1970s to the late 1990s (Clegg et al. 2002; SEER 2002). An estimated 203,500 new invasive breast cancer diagnoses are expected in the United States this year, 54,300 *in situ* cases, and 45,000 deaths (ACS 2002). About 40% of new invasive cases are diagnosed in women younger than 60 years of age (ACS 1996), and breast cancer is the leading cause of cancer death among women 35–54 years of age (National Center for Health Statistics 1997).

The threat to women in mid life coupled with observations of substantial temporal and geographic variation and poor prediction of individual risk has prompted a search for modifiable risk factors. Because breast cancer risk changes over time and varies across geographic locations, factors associated with these variations may provide clues that can lead to prevention. Thus far, many correlates of risk have been identified, including a constellation of hormone-related reproductive factors. These factors account for a substantial portion of the variation in incidence, while also providing evidence that additional factors, probably modest in magnitude, remain to be discovered.

Taken together, epidemiologic studies of hormonal factors in breast cancer and animal studies of the hormonal activity and carcinogenic potential of certain synthetic chemicals suggest environmental pollutants as possible sources of risk. Compounds identified in laboratory studies as mammary carcinogens or hormonally active are in common commercial products and are ubiquitous pollutants to which women in industrial societies are widely exposed, so identifying effects on breast cancer has the potential for substantial public health impact, even if the relative risk associated with exposure is low.

In this article we identify promising leads in the study of environmental pollutants and breast cancer and the challenges in pursuing them. As background, we provide an overview of incidence trends and well-established and suggested breast cancer risk factors that inform environmental research. We review animal studies of chemicals that may be breast carcinogens, promote growth of breast cells and hormonally sensitive tumors, or affect mammary gland development and susceptibility. We assess current knowledge from the few epidemiologic studies of environmental pollutants, discuss the barriers to further progress, and identify research needs.

Background

Trends in incidence and mortality. The association between breast cancer risk and industrial development, historically and worldwide, is one indicator of modifiable risk. Increased access to mammography and other forms of screening is generally believed to play a role in rising incidence, particularly during the early to mid-1980s, but does not explain increases in risk before 1980 or increasing risk for younger and older women who are less likely to be screened or in developing countries with low screening rates (Ursin et al. 1994).

Currently, incidence is rising most rapidly in low-risk populations both internationally (Parkin et al. 2001) and in the United States (SEER 2002), suggesting that ongoing cultural change is a primary contributor. For example, incidence for Asian-American women at the beginning of the 1990s was 40% lower than for U.S. non-Hispanic white women but increased 19% by 1998 compared with 7% increase for non-Hispanic whites (SEER 2002).

In Los Angeles County, California, where ethnic diversity allows for more detailed analysis of trends in ethnic populations, incidence among non-Hispanic whites is 20% higher than for African Americans and roughly double the rate for Hispanics and Asian Americans; in contrast, the rates of change are highest among Asian Americans. Los Angeles County breast cancer incidence rose by 1.1% per year in 1993–1997 among non-Hispanic whites, 2.1% in Hispanics, and 4.6% in Asians, while declining by 0.3% for

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This work was supported by the Boston affiliate of the Susan Komen Breast Cancer Foundation, the Kohlberg Foundation, and the Susan Bailis Breast Cancer Research Fund. We thank S. Gray and C. Willoughby for assistance in monitoring research literature, and C. Willoughby for editorial assistance.

The authors declare they have no conflict of interest.

Received 4 March 2003; accepted 19 May 2003.

African Americans (Deapen et al. 2002). By the late 1990s, rates for women of Japanese and Filipino heritage were approaching rates for non-Hispanic whites.

Surveillance data for Asian-American women are consistent with studies of migrant populations showing that when women migrate from low- to high-risk countries and vice versa, their risk and the risk in successive generations change to approximate the levels in the destination country (Kliewer and Smith 1995). Further, a population-based case–control study of Asian migrants to California and Hawaii showed higher risk associated with longer residence in the United States (Ziegler et al. 1993); and for U.S.-born Asian women, the study showed higher risk for those with more U.S.-born grandparents, an indicator of acculturation. The relative risk associated with migration changed only slightly after controlling for menstrual and reproductive factors, providing evidence that other factors contribute to migration effects (Wu et al. 1996).

Although migration studies provide insight into the contribution of sociocultural factors and support the idea that heritable factors are not predominant determinants of breast cancer risk, studies of heritable genes add a complementary perspective. Mutations in the breast cancer genes *BRCA1* and *BRCA2* are estimated to account for fewer than 10% of cases (Claus et al. 1996), although additional genes that affect hormone synthesis and metabolism and DNA repair likely add to heritable risk (Martin and Weber 2001). The effect of the broader range of heritable genes is seen in studies of identical (monozygotic) and fraternal (dizygotic) twins. In a study of 45,000 twin pairs, 14% of monozygotic twins and 9% of dizygotic twins were concordant for breast cancer diagnosis (Lichtenstein et al. 2000), and Mack et al. (2002) reported slightly higher concordance.

Reproductive and other previously studied risk factors. The fact that reproductive characteristics affect breast cancer risk has been known since 1700, when Ramazzini reported higher incidence among nuns (Spratt et al. 1995). Factors now known to confer higher risk include older age and being female, younger at menarche, older at menopause, nulliparous, and older at a first live birth or stillbirth; whereas higher parity, longer lactation, and bilateral ovariectomy are protective (Davis et al. 1997; Kreiger et al. 1999; Parazzini et al. 1997).

Reproductive risk factors are associated with exposure to estradiol, progesterone, and other hormones; and reproductive hormones are also believed to underlie increased risk associated with alcohol consumption, lack of physical activity, higher body mass index and weight gain after menopause, and low premenopausal body mass index (Bernstein et al. 2002). In addition, recent studies provide some evidence that *in utero* hormonal exposures characteristic of certain pregnancies affect breast cancer risk in the offspring. Daughters exposed to lower hormone levels in pregnancies with toxemia or pre-eclampsia are at lower breast cancer risk, whereas higher hormone levels in pregnancies with twins result in higher risk (Bernstein et al. 2002). This is a new area of research with some inconsistencies within the limited number of studies completed.

Pharmaceutical hormones similarly affect risk. Both estrogen-only and estrogen-progesterone hormone replacement therapy (HRT) for postmenopausal women increase breast cancer risk. In a pooled analysis of 51 studies involving about 54,000 postmenopausal women, the relative risk of breast cancer for women with at least 5 years of recent use was 1.35 [95% confidence interval (95% CI), 1.21–1.49] (Collaborative Group on Hormonal Factors in Breast Cancer 1997). Women who stopped using HRT more than 5 years before were not at higher risk. Additional large-scale population-based epidemiologic studies show 10% increased risk after 5 years of use for estrogen alone and 40% after 15 years, and 30% increased risk for less than 5 years of use for combination HRT (Bernstein et al. 2002). In a clinical trial of combination HRT versus placebo, the Women's Health Initiative reported a hazard ratio of 1.26 (95% CI, 1.00–1.59) about 5 years after enrollment and higher risk for women with prior HRT use up to a hazard ratio of 1.81 (95% CI, 0.6–5.43) (Women's Health Initiative Investigators 2002). For oral contraceptives, recent, but not long-term, use is associated with higher risk (Bernstein 2002), with about 26% increased risk for current users (Collaborative Group on Hormonal Factors in Breast Cancer 1996). Additional information will become available as more women with long-term oral contraceptive use reach the ages of higher breast cancer risk. Diethystilbestrol (DES), a potent synthetic estrogen, has been linked to increased breast cancer risk in women who took DES during pregnancy (Colton et al. 1993; Titus-Ernstoff et al. 2001).

Diet seems very likely to affect breast cancer risk, as it does in animals, but epidemiologic studies have failed to identify specific dietary constituents that increase or decrease risk. Effects of fat and fruits and vegetables have been extensively studied, so far providing no consistent evidence of dietary risk factors (Gandini et al. 2000; Holmes et al. 1999; Hunter and Willett 1996; Michels 2002; Smith-Warner et al. 2001; Willett 1999). High soy intake in Asia has been proposed as a factor in reduced breast cancer rates there, although epidemiologic studies so far provide limited evidence of a protective effect (Adlercreutz 2002; Hilakivi-Clarke et al. 2001; Trock et al. 2000). One recent study of Asian Americans reported a protective effect for soy that was most pronounced for high soy intake beginning in adolescence (Wu et al. 2002), and this study illustrates newer approaches to diet that explore possible effects of the timing of exposure. Other new approaches focus on possible interactions of multiple aspects of diet, for example, alcohol and folate (Feigelson et al. 2003; Zhang et al. 2003), or between diet and genetic polymorphisms (Zheng W et al. 2002).

Ionizing radiation is a clearly established environmental cause of breast cancer (NRC 1990). Studies of atomic bomb survivors and women exposed to X-ray medical treatments in childhood indicate that exposures early in life impart greater risk than adult exposures. In studies of exposed Japanese women 35 years after the atomic bomb, risk of breast cancer was 4-fold greater in women younger than 4 years of age and 2-fold greater in women 10–14 years of age compared with women 20–30 years of age at the time of the bombing. Women younger than 40 years of age had a greater risk than those older than 40 at the time of bombing (Land 1995; Tokunaga et al. 1987).

Higher socioeconomic status (SES), usually measured by education level and income, is consistently associated with higher breast cancer risk, although education and income clearly are not themselves causal. This relationship is often seen even after controlling for breast cancer risk factors such as parity and age at childbearing, which are themselves associated with SES. The possibility that some part of this relationship is due to chemical exposures, for example, from use of consumer products and pesticides, warrants further study. In a small exploratory survey of breast cancer risk factors in high- and low-incidence neighborhoods, higher SES women reported significantly higher use of several different pesticides (home and lawn chemicals, repellents, and lice control) and of dry cleaning (Maxwell et al. 1999).

Role of previously studied risk factors in incidence patterns. Women diagnosed with breast cancer, as with other diseases, often ask themselves, Why me? In recent years, communities with high incidence have struggled with that question as well. A few studies have tried to address these questions at both the individual and population levels, and these studies are interesting because unexplained variation can motivate and inform studies of new hypotheses.

At the individual level, Gail et al. (1989) developed a model that predicts risk from a woman's age, age at menarche, age at first live birth, number of previous biopsies, and

number of first-degree relatives with breast cancer; and this model has been used, among other things, as a basis for identifying women considered high risk as candidates for chemoprevention trials of treatments such as tamoxifen and raloxifene. Using data on breast cancer incidence and risk factors in two large national surveys, Madigan et al. (1995) estimated that 41% of breast cancer risk in the United States is explained by later childbearing, nulliparity, higher income, and family history of breast cancer.

Regarding geographic patterns within the United States, mortality is highest in the Northeast and West and intermediate in the Midwest compared with the South (National Cancer Institute et al. 1999). Sturgeon et al. (1995) reported in an ecologic analysis that recognized breast cancer risk factors accounted for nearly all regional variation in mortality among women younger than 50 years of age; however, among older women, adjustment reduced excess incidence by 50% for the Northeast and Midwest and 10% for the West compared with the South. A similar analysis of the Nurses' Health Study improved on the Sturgeon et al. method by adjusting at the individual level rather than regional level for established risk factors (Laden et al. 1997). However, little variation in breast cancer risk across regions was observed either before or after adjustment, perhaps due to the relative homogeneity in the risk-factor profile of nurses nationwide, so results are not informative.

The extent to which known breast cancer risk factors account for geographic variation is a subject of particular interest in areas such as Cape Cod, Massachusetts, and Marin County, California, where incidence is higher than in a comparison population such as the entire state. Surveillance data show about 20% higher risk on Cape Cod in 1982–1994 (Silent Spring Institute 2000), and case–control data from a statewide study (the Collaborative Breast Cancer Study) show about 20% excess risk for Cape Cod women older than 50 years of age compared with others in Massachusetts, after controlling at the individual level for many recognized and hypothesized breast cancer risk factors (Silent Spring Institute 1998).

In Marin County, where elevated rates of breast cancer were first reported in the 1990s, incidence increased 6 times faster than statewide during the 1990s, rising 3.6% per year (Clarke et al. 2002). A comparison of Marin County with California census block groups that were comparable for census characteristics associated with breast cancer risk showed similar incidence rates in block groups with similar percentage white population, urban status, average parity, median household income, percentage with a college degree, percentage with a working class occupation, and percentage below the poverty line (Prehn and West 1998). Another study reached similar conclusions but relied on risk factor data for women 20–55 years of age, an age group unlikely to be representative of most women with breast cancer, who tend to be older (Robbins et al. 1997). Analysis of demographic factors is not a stopping point for analysis of rate variations, however, because the SES variables are not explanatory for disease.

Aside from the role of established breast cancer risk factors, higher rates of screening mammography could contribute to higher reported incidence in a region. For both Cape Cod and Marin County, available evidence from patterns of stage at diagnosis (based on the expectation of more early-stage diagnoses with mammography) and surveys of mammography use, although not conclusive, is on the whole not consistent with screening as an explanation for higher incidence (Clarke et al. 2002; Silent Spring Institute 1998).

An earlier experience in Marin County illustrates the public health value of drawing etiologic clues from geographic variation. Rapidly increasing incidence of endometrial cancer in Marin County and other affluent neighborhoods in the San Francisco Bay Area led to the identification in the 1970s of estrogen HRT as a causal factor (Austin and Roe 1979).

Insights from Animal Studies

Epidemiologic studies that consistently show increased risk associated with multiple sources of exposure to endogenous and pharmaceutical estrogen and other hormones strongly point to the hypothesis that hormonally active agents in commercial products and pollution also increase risk. Studies in laboratory animals, *in vitro* assays, and wildlife provide further evidence of mechanisms for effects of environmental pollutants on breast cancer risk through exposure to compounds that mimic or disrupt hormones that promote or inhibit tumor growth, act as breast carcinogens, or affect the development and vulnerability of the breast. Although the processes by which breast cancers develop are poorly understood, a review of the primary features of mammary gland development and the effects of hormones and chemicals on mammary gland carcinogenesis in animal models shows that the mechanisms that underlie the recognized risk factors for breast cancer in humans are also seen in animal studies. This section outlines current research related to biological mechanisms for breast cancer, including chemical and hormonal factors and the hypothesis that hormonally active chemicals—also known as endocrine disruptors—affect breast cancer. This information provides the essential scientific foundation for evaluating existing hypotheses about environmental factors in breast cancer and generating new hypotheses and directions for future research.

Mechanistic models for cancer. Historically, carcinogenesis has been characterized by three separate stages: initiation, promotion, and progression. Although the process of carcinogenesis is now recognized as more complex than this simple model suggests, the three-stage model still provides a useful paradigm by which chemicals can be described based on a potential mechanism of action (Barrett 1993; Pitot et al. 2000). Initiation is characterized as an irreversible change in a cell, very probably a genetic change or mutation, resulting in a latent neoplastic cell (Appel et al. 1990; Pitot 1993; Pitot and Dragan 1991). Promotion is the process by which an initiated cell expands clonally into a visible, benign tumor (Barrett 1993). Experimental evidence demonstrates that chemically modulated promotion of a cell requires repeated exposure; endogenous estrogen is thought to affect the process of mammary carcinogenesis primarily by this mechanism. Progression is the term used to describe the irreversible transition from a benign to malignant tumor, which involves additional genetic events, although not necessarily point mutations in DNA (Barrett 1993; Pitot 1993; Pitot and Dragan 1991).

Agents that are carcinogens are often genotoxic, or able to damage DNA. Both initiation and progression steps involve some level of genotoxicity, whereas tumor promotion more typically involves stimulation of cell proliferation. Many agents stimulate cell proliferation, and there is controversy over whether these should be considered carcinogens unless they can also induce some level of genetic damage (Alden 2000; Klaunig et al. 2000). Of course, increasing cell proliferation also increases the opportunity for spontaneous mutations, so even promoters can have some impact on DNA integrity.

Another model for carcinogenesis focuses on cell–cell interactions that maintain tissue organization in normal tissue and break down in carcinogenesis (Sonnenschein and Soto 1999). The role of stromal cells in inhibiting or promoting carcinogenic progression in breast epithelia is an ongoing area of research (Barcellos-Hoff 2001; Barcellos-Hoff and Ravini 2000; Mueller et al. 2002), and this work suggests that the study of chemical carcinogenesis must consider effects on cell signaling as well as traditional genotoxic effects.

Mammary gland development and susceptibility. The breast is one of the few organs that is not fully developed at birth. It reaches its fully differentiated state only through the hormonal stimuli induced by pregnancy and lactation, resulting in portions of the life cycle with increased susceptibility to carcinogens. Aspects of development that

are known to affect gland susceptibility include rates of cell proliferation, stages of cell differentiation, and prenatal imprinting of hormonally sensitive tissues.

Greater susceptibility to genotoxic agents is expected during periods of rapid breast cell proliferation, such as prenatal, perinatal, and pubertal time periods and during pregnancy (Russo and Russo 1996; Wolff et al. 1996). Rodent studies of dimethylbenzanthracene (DMBA)-induced mammary tumors have shown a greater number of tumors and shorter latency when the carcinogen is administered to immature animals (Dunnick et al. 1995). Similar findings of increased risk for earlier age at exposure are observed in human studies of atomic bomb survivors (Tokunaga et al. 1987).

In addition to susceptibility during periods of cell proliferation, the susceptibility of the mammary gland to carcinogen exposure decreases after the first full-term pregnancy, when formerly undifferentiated cells have developed into fully differentiated cells, which are less susceptible to genetic damage and subsequent propagation of the damaged cell (Neumann et al. 1996; Russo and Russo 1996; Wolff et al. 1996). Epidemiologic studies have consistently shown that early age of first full-term pregnancy is a protective factor for breast cancer, and studies in animal models demonstrate that virgin rats are significantly more susceptible to chemically induced mammary gland cancers than are age-matched parous rats, which are relatively resistant to tumors (Brisken 2002; Russo and Russo 1998). Indeed, ductal and lobular carcinomas tend to originate from undifferentiated cells, whereas benign breast tumors tend to originate from the more differentiated cells (Russo and Russo 1996). Characterizing the specific hormonal factors that are responsible for the refractoriness of mammary glands postpregnancy is a topic of ongoing research (Brisken 2002; Sivaraman and Medina 2002).

Because the breast is particularly susceptible to carcinogen exposure up until the first full-term pregnancy, there may be an interaction between risk associated with age at first pregnancy, an established breast cancer risk factor, and risk associated with chemical exposure. In other words, in a hypothetical group of women with similar lifetime exposures to a mammary carcinogen beginning in childhood, those who were youngest at their first full-term pregnancy would experience the lowest increase in risk, and those who were oldest would experience the greatest increase in risk.

In addition, a number of studies in humans and animal models suggest that the *in utero* environment affects subsequent breast cancer risk in offspring (see preceding discussion of human studies). Animal studies have shown that administration of estradiol or DES during pregnancy increases breast cancer rates in female offspring (reviewed in Hilakivi-Clarke et al. 2001). One mechanism that has been proposed involves imprinting of mammary gland tissues *in utero*, resulting in an effect on the responsiveness of the tissues to estrogen later in life.

Hormonal factors in mammary carcinogenesis. Throughout the life cycle, the hormonal environment plays a critical role in the development of breast cancer. Removal of both ovaries reduces risk, and increased risk has been observed for women with higher levels of endogenous and pharmaceutical estrogen exposure (Henderson and Feigelson 2000). In animal studies, treatment with chemical carcinogens does not produce mammary tumors in the absence of endogenous hormones (Russo and Russo 1996, 1998). In other words, animals that have had their ovaries removed do not develop mammary tumors even after exposure to carcinogens. Supplementing animals with extra estrogens produces tumors even in the absence of specific chemical exposures (Russo and Russo 1996, 1998). These findings are consistent with the idea that estrogens are promoters of mammary tumors, which act over a long period of time by causing cell proliferation and clonal expansion of initiated cells. In addition, estrogens appear to be required for mammary carcinogenesis to occur.

Studies of normal mammary gland development and chemically induced mammary carcinogenesis in animal models have provided useful information for clarifying how the interplay of ovarian, pituitary, and placental hormones, while influencing the structure, organization, and function of the mammary gland, modulate its response to chemical carcinogens. Many hormones and growth factors have been demonstrated to affect the tumorigenic response of rats to genotoxic mammary carcinogens, including ovarian, placental, pituitary, and thyroid hormones, as well as androgens, insulin, and many growth factors (Brisken 2002; Neumann et al. 1996; Russo and Russo 1998; Sivaraman and Medina 2002; Swanson and Unterman 2002). In human studies, androgens and insulin-like growth factor 1 have been shown to be associated with risk of breast cancer (Toniolo et al. 2000; Wang et al. 2000).

Some researchers characterize certain estrogens, including the primary active endogenous estrogen 17β-estradiol, common pharmaceutical estrogens, and the synthetic estrogen DES, as carcinogens on the basis of their significant role in hormonally mediated cancers in humans and animals (Tsutsui and Barrett 1997). Others do not consider endogenous hormones to be carcinogenic themselves but acknowledge their role as promoters of carcinogenesis because they allow neoplastically transformed cells initiated by other carcinogens to establish and grow by modifying the target tissue (Russo and Russo 1996, 1998). In addition to acting as promoters, DES, 17β-estradiol, and certain metabolites of 17β-estradiol, including 16β-hydroxyestrone, have been shown to exhibit specific types of genotoxic activity under certain conditions (Liehr et al. 1990; Telang et al. 1992; Tsutsui and Barrett 1997). Steroidal estrogens are listed as known human carcinogens in the *Report on Carcinogens, Tenth edition* by the U.S. National Toxicology Program (NTP 2002).

Chemical factors in mammary carcinogenesis. Experimental studies in animals offer an alternative means for identifying potential carcinogens in the environment, given that epidemiologic studies require a large number of women, a long duration, and adequate exposure information. The NTP has studied the carcinogenic potential of about 500 chemicals in animal carcinogenicity bioassays. Of these chemicals, 42 caused mammary tumors in the tests (Bennett and Davis 2002; Dunnick et al. 1995). These are listed in Table 1, along with information about their common uses. These chemicals include halogenated chemicals and solvents, including components of gasoline; aromatic amino/nitro compounds; dyes; and epoxides. Other research organizations that have conducted animal carcinogenicity bioassays on specific chemicals have identified about 160 additional chemicals as mammary carcinogens (Wolff et al. 1996). These include, for example, products of combustion [polycyclic aromatic hydrocarbons (PAHs), nitro-PAHs], ionizing radiation, common industrial solvents and other industrial chemicals (vinyl chloride, vinyl fluoride, vinylidene chloride, styrene, acrylamide), pesticides (atrazine, dichlorvos), and other substances (IARC 1999; Pinter et al. 1990). Many of the chemicals identified as mammary carcinogens in these bioassays also show evidence of genotoxicity. For example, in their review of 34 chemicals identified as mammary carcinogens by the NTP, Dunnick et al. (1995) report that 26 showed evidence of mutagenicity in the *Salmonella* assay.

Chemicals identified as mammary carcinogens in animal studies are priorities for follow-up study in humans. Only four of the 42 chemicals tested by the NTP (benzene, 1,3-butadiene, ethylene oxide, C.I. acid red 114) have adequate human evidence of carcinogenicity to be classified as carcinogenic in humans (NTP 2000). Although the breast is not the primary tumor site for any of these four chemicals, many of the human cohorts studied were all or predominantly male, and

some limited epidemiologic evidence supports the breast as a tumor site for ethylene oxide (the sterilant) and benzene (in gasoline) (see additional discussion further below) (Hansen 2000; Petralia et al. 1998; Tompa et al. 1999). In addition, some animal mammary carcinogens identified in other testing programs also have epidemiologic evidence of breast cancers from occupational studies, including, for example, methylene chloride, PAHs, and chlorinated solvents (Hansen 1999, 2000; IARC 1999; Petralia et al. 1999).

Potential role of hormonally active chemicals. Recent research sheds light on a class of hormonally active chemicals, referred to as endocrine disruptors, that may affect breast cancer primarily by promotional mechanisms, as well as by affecting mammary gland development and responsiveness to other carcinogens. The hypothesis has been put forward that exposure to endocrine disruptors, including chemicals that mimic estrogens, might play a role in breast cancer risk (Davis et al. 1993). To date, more than 500 chemicals have been found to be weakly estrogenic in various assays, including many chemicals in common use, such as constituents of detergents, pesticides, and plastics (Jobling et al. 1995; Nishihara et al. 2000; Soto et al. 1995). Table 2 lists selected classes of these chemicals, specific examples, and common uses. Many of these chemicals have been shown to mimic estrogen in a variety of short term *in vitro* assays; they bind the estrogen receptor, initiate transcription of estrogen-regulated genes, and can stimulate breast cancer cells *in vitro* to proliferate (Korach and McLachlan 1995; Shelby et al. 1996; Soto et al. 1995). Short-term *in vivo* assays, such as increase in uterine weight in rodents, are also used to demonstrate estrogenic activity (O'Connor et al. 1996). In addition, effects of these compounds have been frequently observed in wildlife; for example, widespread sexual disruption of wild fish has been reported in rivers receiving wastewater effluent, which contains a mixture of endogenous and pharmaceutical estrogens and industrial chemical endocrine disruptors (Jobling et al. 1998).

Table 1. Chemicals associated with increased incidence of mammary gland tumors in rats and/or mice in testing by the NTP.[a]

Chemical	Use
Acronycine	Pharmaceuticals
Benzene[b]	Gasoline, solvent
2,2-bis(Bromomethyl)-1,3-propanediol	Flame retardant
1,3-Butadiene[c]	Auto exhaust, rubber manufacture, gasoline
C.I. acid red 114[c]	Dye for silk, jute, wool, leather
C.I. basic red 9 monohydrochloride[d]	Dye for textiles, leather, paper, biological stain
2-Chloroacetophenone	Flame retardant
Chloroprene[d]	Used in neoprene manufacture
Clonitralid	Molluskicide
Cytembena	Pharmaceuticals
2,4-Diaminotoluene[d]	Intermediate in dye synthesis
1,2-Dibromo-3-chloropropane[d]	Soil fumigant, pesticide
1,2-Dibromoethane[d]	Soil fumigate, lead scavenger in gasoline
2,3-Dibromo-1-propanol	Flame retardant
1,1-Dichloroethane	Solvent
1,2-Dichloroethane	Solvent, chemical intermediate in insecticide formulations, gasoline
1,2-Dichloropropane (propylene dichloride)	Chemical intermediate, solvent in dry cleaning fluids, fumigant
Dichlorvos	Pesticide
1,2-Dimethoxybenzidine dihydrochloride[d]	Dye intermediate
3,3′-Dimethylbenzidine dihydrochloride	Dye intermediate
2,4-Dinitrotoluene	Dye intermediate, explosives, propellants
Ethylene oxide[b]	Sterilizing gas for medical equipment
Furosemide	Pharmaceutical
Glycidol[d]	Stabilizer in vinyl polymers, intermediate in pesticides and fragrances
Hydrazobenzene[d]	Dye intermediate, tobacco pesticides, motor oil
Isophosphamide	Pharmaceuticals
Indium phosphide	Microelectronics, semiconductors, injection lasers, diodes
Isoprene	By-product of ethylene production
Methylene chloride	Solvent, furniture stripper, adhesives
Methyleugenol	Food additive, flavoring, also naturally occurring
Nithiazide	Antiprotozoal compound
5-Nitroacenaphthene	Research chemical
Nitrofurazone	Antibiotic
Nitromethane	Rocket and engine fuel, solvent, mining explosive
Ochratoxin A[d]	Mycotoxin
Phenesterin	Pharmaceuticals
Procarbazine hydrochloride[d]	Pharmaceuticals
Reserpine[d]	Pharmaceuticals
Sulfallate[d]	Herbicide
2,4- and 2,6-Toluene diisocyanate[d]	Used in manufacture of flexible polyurethane foams
o-Toluidine hydrochloride[d]	Dye intermediate
1,2,3-Trichloropropane[d]	Chemical intermediate, former solvent and paint remover

Data from Bennett and Davis (2002), Dunnick et al. (1995), IARC (1999), and NTP (2000).
[a]Listed chemicals caused cancer in mammary glands in one or more of the four typical gender–species experiments conducted on each chemical (i.e., male rats, female rats, male mice, female mice); for example, benzene caused mammary gland tumors in female mice, whereas glycidol induced tumors of the mammary gland in male and female rats and in female mice. Overall number of chemicals evaluated in NTP long-term carcinogenesis experiments, 500. Animal mammary carcinogens that were not studied by the NTP are not listed (e.g., PAHs, nitro-PAHs, ionizing radiation, vinyl chloride, vinyl fluoride, vinylidene chloride, atrazine, styrene, acrylamide; and others). [b]Listed as "known human carcinogen" in *Report on Carcinogens, Ninth edition* (NTP 2000); some epidemiologic evidence of breast cancer. [c]Listed as "known human carcinogen" in *Report on Carcinogens, Ninth edition* (NTP 2000). [d]Listed as "reasonably anticipated to be human carcinogen" in *Report on Carcinogens, Ninth edition* (NTP 2000).

As research in this area continues to identify estrogenic compounds, significant questions are raised about how to evaluate the potential adverse health effects (Rudel 1997). These questions are far from being resolved. On the one hand, the potency of many of these endocrine-disrupting pollutants is typically much lower than the potency of endogenous estrogens, and so it has been proposed that their effects will be insignificant (Safe 1995). On the other hand, there is particular concern about the effects of endocrine-disrupting chemicals for exposures that take place when levels of endogenous hormones are very low, such as *in utero* or during prepubertal, or postmenopausal time periods. Also, a number of studies have demonstrated that multiple estrogenic chemicals can act together to produce an effect even when each individual component of the mixture is present below a threshold for effect, so these pollutants can act in combination (Silva et al. 2002). Finally, comparison of the *in vivo* estrogenic effects of a range of compounds demonstrates that estrogenic compounds exhibit diversity in both mechanism and effects (Gould et al. 1998; Rudel 1997). This diversity is attributed, at least in part, to the fact that the shape of the estrogen receptor ligand (either estradiol or an endocrine disruptor) affects the binding of the receptor–ligand complex to DNA sequences and subsequent gene expression. Current research into pharmaceutical selective estrogen response modifiers (SERMs) for menopause and breast cancer prevention is an outgrowth of this phenomenon (Emmen and Korach 2001). Recent discovery of a second estrogen receptor, ER-β, complicates matters further because many hormonally active compounds have differential binding affinities for the two receptors, and cellular responses to such stimuli are difficult to predict (Pennie

et al. 1998). Thus, just because two estrogenic chemicals cause a similar effect on one outcome (e.g., uterine weight) does not mean they will cause a similar effect on all estrogen receptor–mediated outcomes.

It is of particular interest that certain dietary constituents that have been hypothesized to be preventive of breast cancer, such as genistein in soy, are also estrogenic in many endocrine disruptor screening bioassays (Adlercreutz et al. 1995). As discussed above, the relationship between soy food intake and breast cancer risk in humans is controversial. In animal studies, genistein treatment often, but not always, reduced the rate of breast cancer, with the effect being strongest with treatment before puberty (Hilakivi-Clarke et al. 2001). It is hypothesized that the genistein treatment before puberty mimics the effect of an early pregnancy (this effect has been demonstrated with estradiol also), thus reducing the susceptibility of the mammary gland to carcinogenesis (Hilakivi-Clarke et al. 2001). Additional data from animal and *in vitro* studies suggest that phytoestrogens such as genistein have mixed estrogen agonist/antagonist activity and can inhibit the biological response to endogenous estrogens, although this apparent antagonist action may not take place directly via the estrogen receptor or may be due to the differential binding of genistein to ER-α and ER-β (An et al. 2001; Ford 2002; Fotsis et al. 1993; Lamartiniere et al. 1995; Markaverich et al. 1995; Po et al. 2002). This remains an active area of research.

Table 2. Selected endocrine-disrupting chemicals.

Compound	Exposures/uses
Pesticides	
Atrazine	Selective herbicide
Chlordane	Insecticide, acaricide, veterinary pharmaceutical
Chlorpyrifos	Insecticide, acaricide
Cypermethrin	Insecticide
2,4-Dichlorophenoxyacetic acid	Herbicide
DDT (and associated compounds)	Contact insecticide
Dieldrin, aldrin, endrin	Formerly as insecticide
Lindane	Insecticide
Malathion	Insecticide
Methoxychlor	Insecticide, veterinary pharmaceutical
Pentachlorophenol	Insecticide for termite control, wood preservative
Permethrin, sumithrin	Insecticide
Toxaphene	Insecticide
Tributyl tin (chloride)	Biocide, rodent repellent
Vinclozolin	Agricultural fungicide
Persistent nonpesticide OCs and PAHs	
PAHs	Compounds present in industrial air pollutants, smoke from coal or coke-burners, tobacco tar, some foods
Polybrominated biphenyls	Formerly as flame retardant
Polybrominated diphenyl ethers	Flame retardants
PCBs (Aroclor 1254)	No longer produced commercially—since 1974, in closed electrical capacitors and transformers; before 1972, in transformers and other electrical equipment, carbonless copy paper
Dioxins and furans	Produced during incineration, paper manufacturing, and production of chlorine aromatics; impurity in some herbicides
Phenols and alkylphenols	
Bisphenol A	Polycarbonate and polyester–styrene resins
4-*tert*-Butylphenol	Intermediate in the manufacturing of varnish and lacquer resins, soap antioxidant
Nonylphenol polyethoxylate, 4-nonylphenol, 4-octylphenol	Surfactant, detergent, defoaming agent, some pesticide formulations, degradation product of alkylphenol ethoxylated antioxidant in some plastics
o-Phenylphenol	Disinfectant fungicide, in the rubber industry
Phthalates	
bis(2-Ethylhexyl) phthalate, butyl benzyl phthalate	Commonly used plasticizer for polyvinyl chloride polymers
Di-*n*-butyl phthalate, diethyl phthalate	Personal care products such as nail polish, perfume, hair spray, plasticizers, inks, adhesives, other uses
Parabens	
Butyl, ethyl, methyl, propyl paraben	Pharmaceutical aid (antifungal), preservative in foods; in creams, lotions, ointments, other cosmetics
Other organics	
Amsonic acid	In manufacturing of dyes, bleaching agents, optical brighteners or fluorescent whitening agents
Styrene	Manufacturing plastics, synthetic rubber, resins; insulator
Vinyl acetate	Used in the production of a wide range of polymers, including polyvinyl acetate, polyvinyl alcohol; widely used in production of adhesives, paints, food packaging
Metals	
Cadmium, lead	Batteries, plastic stabilizers, pigments
Mercury	Thermometers, dentistry, pharmaceuticals, agricultural chemicals, antifouling paints, many other uses
Phytoestrogens	
Genistein, coumestrol, zearalenone	Soy, grains, grain molds

Data from Budavari (1996), Harris et al. (1997), IARC (1998), Illinois Environmental Protection Agency (1997), Routledge et al. (1998), Smith and Quinn (1992), Soto et al. (1995), and SRI International (1995).

Another new and important area of research related to hormonally active chemicals concerns imprinting of the mammary gland from *in utero* exposures to hormones or hormonally active chemicals. As discussed above, animal studies and limited human studies have shown that *in utero* exposure to estradiol or DES increases mammary tumor formation in the offspring (reviewed in Hilakivi-Clarke et al. 2001). In experiments related to dietary constituents, maternal intake of fatty acids and genistein, but not soy, increased DMBA-induced mammary carcinogenesis in the offspring (even though the soy diet increased pregnancy estrogen levels) (Hilakivi-Clarke et al. 2001). Limited research has been conducted on the effects of *in utero* exposures to environmental chemicals on mammary gland development and carcinogenesis (reviewed in Birnbaum and Fenton 2003). However, two studies of *in utero* exposure of rats to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) show effects on mammary gland development, and one shows increased susceptibility to chemically induced mammary tumors (Brown et al. 1998; Fenton et al. 2002). In addition, increased susceptibility to chemically induced mammary tumors was observed in one study of a mixture of organochlorines [OCs; e.g., dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE), polychlorinated biphenyls (PCBs)] given neonatally to rats (Desaulniers et al. 2001), and gestational exposure to atrazine and bisphenol A have also been shown to affect mammary gland development in rodents (reviewed in Birnbaum and Fenton 2003). It is interesting to note that all of the compounds that have been shown to affect mammary gland development after gestational exposure possess some type of direct endocrine-modulating activity (e.g., estrogen agonist, androgen antagonist, etc.).

Endocrine disruptors can also act indirectly, for example, by up- or down-regulating the enzymes that metabolize endogenous estrogens or by affecting synthesis

of endogenous hormones (NRC 1999). For example, effects of alcohol on breast cancer are hypothesized to be due to a variety of impacts on cellular signaling pathways, including increased circulating estrogen and androgen levels (Ginsburg et al. 1995; Singletary and Gapstur 2001). Although the focus of research in this area has been on measuring circulating serum or urinary levels of endogenous hormones, it is important to note that human breast tissue can metabolize hormones and create its own local hormonal environment independent of circulating levels (Adams 1991; Adams et al. 1992). Thus, effects of chemicals on the local hormone environment in the breast may be more relevant than effects on circulating hormone levels.

Overall, studies in lab animals, *in vitro* assays, and wildlife help characterize factors that influence breast development and carcinogenesis. These insights in turn inform hypothesis generation for human studies and help interpret findings in these studies. Toxicological research is a critical avenue for achieving breast cancer risk reduction because occupational epidemiology provides little information on women's cancers (see next section). Priorities for toxicologic research are outlined in the final section of this article.

Human Epidemiologic Evidence

Occupational studies. Despite the strength of toxicologic evidence for effects of certain pollutants on breast cancer risk, very little human evidence has accrued. In other areas of cancer research, leads from the laboratory often are first translated into human research in occupational studies where exposures are higher and better characterized compared with community settings, but few occupational studies have included women, so this resource is limited for evaluating breast cancer risk.

Elevated incidence has been observed repeatedly among women in white-collar jobs, due partly to reproductive risk factors, such as later childbearing, that are associated with the higher educational attainment required in these jobs and with higher SES more broadly. In some studies, associations are seen for white-collar jobs after controlling for SES and other possible confounders. For example, Band et al. (2000) observed elevated risk for teachers and medical workers. Calle et al. (1998) reported elevated risk for executives and secretaries but not teachers, librarians, or nurses, in a study that included a crude measure of physical activity, a potentially important source of confounding in studies of occupation and breast cancer. White-collar jobs do involve chemical exposures that may be related to breast cancer, including exposures to indoor pesticides, solvents, second-hand tobacco smoke, and flame retardants (Spengler et al. 2000), but these exposures are so poorly understood that most white-collar job categories are not informative with respect to questions about environmental pollutants.

Few studies have investigated breast cancer risk for women in occupations with more obvious chemical exposures, even among nurses, many of whom have substantial chemical exposures and for whom a large prospective cohort study is already in place (Nurses' Health Study 2002). Nurses are likely to have been exposed to the mammary carcinogen ethylene oxide (NTP 1998), which is used to sterilize medical equipment, and to hormonally active compounds, including nonylphenol (used in detergents and plastics) and bisphenol A (used in polycarbonate plastics) (Aschengrau et al. 1998). Two studies (Norman et al. 1995; Tompa et al. 1999) provide weak evidence of an association between ethylene oxide and breast cancer among nurses.

A few studies provide evidence of breast cancer risk associated with exposures to the mammary carcinogens benzene, PAHs, and certain organic solvents. Hansen (2000) reported higher risk of breast cancer for men exposed to gasoline and vehicular combustion products, benzene, 1,2-butadiene, 1,2-dibromoethane, 1,2-dichloroethane, and PAHs. With a lag time of at least 10 years, the odds ratio, adjusted for SES, was 2.5 (95% CI, 1.3–4.5) for exposed men, and the relative risk was more than 5-fold for men younger than 40 years of age at diagnosis (odds ratio = 5.4, 95% CI, 2.4–11.9).

Petralia et al. (1999) used interview-based lifetime job histories and a job-exposure matrix to assess women's exposure to benzene and PAHs, adjusted for breast cancer risk factors. Exposed jobs involved bus and truck operators and engine mechanics, molding and casting machine operators, and garage and service-station occupations. PAH exposures independent of benzene are also found in traffic and shipping jobs, and benzene exposures without PAHs are found among clinical laboratory technologists, painters, and sculptors. The highest risk was seen for women exposed to both benzene and PAH, with about 2-fold increased risk for women ever exposed and higher risk for women exposed for 4 or more years. Increased risk of premenopausal breast cancer was seen among women exposed to benzene. The risk of PAH exposure could not be evaluated independent of benzene because of small numbers. Results provide some evidence of higher risk with longer duration of exposure and a latency period of 20 or more years.

Organic solvents, many of which are animal mammary carcinogens, have also been associated with breast cancer in an occupational study of 7,802 Danish women diagnosed at 20–55 years of age. Breast cancer risk was increased 20–66%, adjusted for childbearing and SES, for women employed longer than a year in jobs with extensive organic solvent use (Hansen 1999). Exposed women were employed in nonadministrative jobs in industries that involved metal products, wood and furniture, printing, chemicals, and textiles. Risks were more elevated for women who worked more than 10 years in these industries and for analyses with 15 or more years lag time. A 2-fold increased risk was seen for those with more than 10 years of employment.

In a case–control study of 995 incident breast cancers in British Columbia, Band et al. (2000) reported elevated risk among women in job titles associated with exposure to solvents and pesticides. In a study of Shanghai Cancer Registry data, Petralia et al. (1998) found breast cancer standardized incidence ratios (SIRs) were most elevated for women in professional jobs, but SIRs were also 40% higher for women with high probability of exposure to organic solvents and elevated for exposure to benzene and medium and high probability of pesticide exposure, based on a small number of cases. On the basis of "usual occupation" in mortality records for 33,509 cases and 117,794 controls in 24 states in the United States, Cantor et al. (1995) reported higher risk associated with higher probability and level of exposure to styrene; the widely used organic solvents methylene chloride, carbon tetrachloride, and formaldehyde; acid mists; and several metals.

Among 115 earlier studies of occupation and breast cancer reviewed by Goldberg and Labreche (1996), a few notable associations were seen. Two cohort studies reported evidence of higher risk for women in pharmaceutical manufacturing, and higher risk was also reported for women employed as cosmetologists or beauticians. Pollan and Gustavsson (1999) similarly reported elevated incidence for pharmacists, hairdressers, and beauticians with SES controlled in a cohort of women employed in 1970. Both historical and current risk among hairdressers is of interest because the mammary carcinogen vinyl chloride was used in hairspray until the early 1970s. Knowledge of workplace practices, more generally, may lead to better understanding of potentially informative inconsistencies among occupational studies.

Elevated risk was observed in other chemical-exposed jobs among metal platers and coaters (Pollan and Gustavsson 1999), whereas Goldberg and Labreche (1996) found little support for higher breast cancer risk for women in textile production (with exposure to dyes), dry cleaning (with exposure to organic solvents), or the nuclear industry. The negative finding in the nuclear industry

despite clear evidence that ionizing radiation increases risk could mean that most workers were not actually exposed, or it could be due to protective characteristics of the workforce in that setting. For example, some jobs may attract or require women with high levels of physical activity, or sensitive workers may develop acute effects such as dermatitis and central nervous system symptoms that cause them to leave the workplace. This well-known phenomenon, referred to as the "healthy worker effect," complicates interpretation of negative occupational studies.

Similarly, breast cancer risk among farm women is of interest because of possible exposure to pesticides, but in general, observed breast cancer risk is lower among U.S. farm women, perhaps due to greater levels of physical activity or patterns in other established risk factors. Consistent with other studies, the Carolina Breast Cancer Study found that women who lived or worked on a farm had lower risk, but among those who did not wear protective clothing when applying pesticides, a 2-fold higher risk of breast cancer was observed (Duell et al. 2000). Research under way in the Agricultural Health Study will provide much better information about farm-related risk (Alavanja et al. 1994).

Overall, occupational studies provide fairly consistent evidence that elevated risk independent of SES is associated with a few specific exposures—benzene, organic solvents, and PAHs—especially for younger workers, and it is interesting to note that the chemicals with the most consistent human evidence have also been identified as animal mammary carcinogens (Table 1). Leads from previous occupational findings and new directions based on animal studies are priorities for further research, although follow-up studies will be challenging. Some of the challenges are typical of occupational studies; for example, workers are typically exposed to mixtures of chemicals, so specific exposures and exposure histories are difficult to reconstruct. In addition, using surveillance methods that are common in occupational studies makes it hard to separate out the effects of chemical exposures in populations that have protective characteristics, such as higher physical activity or lower-risk reproductive patterns. Other challenges arise from women's typical work histories, with exposed women likely to move into and out of the workforce and to be employed in dispersed, small-scale settings such as beauty shops. Goldberg and Labreche (1996) identify a number of weaknesses common in the studies they reviewed: reliance on administrative data and broad job categories as an indicator of exposure; lack of information on confounders, including childbearing and SES; use of mortality as an outcome rather than incidence, which limits the relevance to etiology; and low statistical power. Concerted efforts to overcome these limitations are important because occupational studies are the primary means by which chemicals become identified as human carcinogens (IARC 1998).

In future studies, possible confounding by work-related physical activity could be assessed using job matrix methods that parallel the assessment of chemical exposures. However, studies that contact workers to assess a broader range of established breast cancer risk factors concurrently with workplace exposures are needed to deal with other potential confounders. These studies will be most useful in evaluating chemical exposures that result in cancers diagnosed during women's working years, and longitudinal follow-up will be required to pick up effects among older women. Studies of health outcomes that are known or suspected to be related to breast cancer risk, including breast density, fertility outcomes, and age at menopause, also provide avenues to learn about breast cancer through occupational studies without waiting for workers to reach the older years when breast cancers are typically diagnosed. The likelihood, based on effect sizes for established breast cancer risk factors, that effects of occupational exposures may be modest in size means that large sample sizes or meta-analysis of multiple studies will be needed to discern effects. As more women move into jobs with substantial chemical exposure, assessment of occupational risks will become even more important.

Population-based studies. Population-based studies have investigated a narrow range of the compounds identified in the toxicologic literature as plausibly relevant to breast cancer. Certain OC compounds (DDT, PCBs) have been most studied; because they are persistent and lipophilic, residues can be measured in adipose tissue and blood years after exposure. Most studies to date have measured residues at the time of diagnosis or interview and assumed that these recent measures can be used as proxies for historical exposures. A few studies have assessed PAHs, some of which are potent mammary carcinogens in animals, and tobacco smoke, mixtures with complex toxicologic properties. Accidental exposures have led to studies of dioxin (TCDD) and perchloroethylene (PCE, also called tetrachloroethylene).

The largest recent report is from the Long Island Breast Cancer Study Project case–control study that assessed PAHs and certain OCs, based on blood samples drawn near the time of diagnosis (cases) or interview (controls) (Gammon et al. 2002a, 2002b). PAH exposure was assessed by measuring PAH–DNA adducts, a measure of DNA damage from exposure over the previous months to a few years. Results showed 49% higher risk, adjusted for breast cancer risk factors, for the highest compared with the lowest quintile of adducts (95% CI, 1.00–2.21), with no evidence of a dose–response relationship (Gammon et al. 2002a). Although the authors expected grilled food and tobacco smoke to be the primary sources of PAH, the lack of relationship between these exposures and PAH–DNA adducts suggests that other sources, for example, air pollution, may be more important. PAH–DNA adducts represent combined effects of intake and individual response, so the lack of dose response could mean that this measure is a better indicator of individual response than exposure (within the range of exposures in this study).

The Long Island study showed no significantly elevated risk associated with lipid-adjusted blood levels of the OC compounds DDE (the primary metabolite of DDT), chlordane, dieldrin, or the sum of the four most common PCB congeners, although small increases in risk were observed for the highest compared with the lowest exposure groups, with no dose–response trend, for DDE, DDT, and dieldrin (Gammon et al. 2002b). No consistent associations were seen for subgroups defined by reproductive risk factors, body size, years of residence on Long Island, or tumor estrogen- or progesterone-receptor status.

The results for DDE are consistent with scientific evidence that accumulated over the years during which the Long Island study took place. Although a few early studies reported an association with breast cancer, only 6 of 27 studies reviewed by Snedeker (2001) reported statistically significant positive associations. In her review, Snedeker offers a potential explanation for the many negative studies. She points out that most studies rely on DDE as an indicator of previous exposure to DDT because DDT is not currently detectable in blood in countries where DDT was banned years ago. However, diet (especially meat, fish, and dairy) is a major ongoing route of exposure to DDE, so DDE levels in blood represent exposure from diet as well as DDE metabolized from previous DDT exposure. DDE is much less hormonally active, so it may be that DDT, but not DDE, contributes to breast cancer, and if exposure to DDT is poorly measured by current blood levels of DDE, studies that rely on DDE are not informative. In fact, a recent study by Hoyer et al. (2000a) showed a significant relationship, with dose response, for breast cancer risk and *p,p′*-DDT measured prospectively in the late 1970s and early 1980s but no association for DDE. In addition, preliminary results from a California study using blood drawn during active DDT use showed increased risk of breast cancer

diagnosed before age 50. Serum levels were measured prospectively in 131 case–control pairs. The odds ratio was 3.9 (95% CI, 1.4–10.9) for the second versus first tertile of DDT and 10.4 (95% CI, 2.5–43.2) for the third versus first tertile, with a highly statistically significant *p*-value for trend (Cohn et al. 2002). Additional studies of DDT levels in women currently exposed around the world or in blood drawn during years when DDT was in use in the United States may be informative.

A series of analyses of the association between breast cancer and blood levels of the pesticide dieldrin in Danish women have shown significant associations and dose–response trends for 1970s blood levels and breast cancer incidence (Hoyer et al. 1998) and mortality (Hoyer et al. 2000b). Mortality was increased more than 5-fold for women with the highest dieldrin levels averaged across two measurements from the 1970s and early 1980s (relative risk = 5.76; 95% CI, 1.86–17.92) (Hoyer et al. 2000b). Subgroup analyses showed the strongest associations with breast cancer risk for estrogen-receptor–negative tumors (Hoyer et al. 2001) and for tumors with *p53* mutations (Hoyer et al. 2002). One potential explanation for these positive findings compared with other OC results is that blood measures were taken closer to the time of dieldrin use, which ended in the late 1970s, so they are better indicators of exposure.

Given the many difficulties of measuring historical exposures and characterizing variation among individuals in community settings, studies of unusual accidental exposures are a valuable resource. In a study of dioxin in women who were infants to 40 years of age at the time of a 1976 industrial accident in Seveso, Italy, Warner et al. (2002) reported a 2-fold increase in breast cancer risk among women with a 10-fold increase in serum level of dioxin (hazard ratio = 2.1; 95% CI, 1.0–4.6). Aschengrau et al. (2002) reported small to moderate increases in risk for women on Cape Cod, Massachusetts, exposed to PCE that leached from vinyl-lined water distribution pipes (adjusted odds ratios = 1.5–1.9 for > 75th percentile with 0–15 years of latency). Both of these studies have significance beyond the accidental exposure scenarios because dioxin and PCE are common exposures in everyday settings that could be reduced through changes in public policy. Dioxin is a widespread environmental contaminant, for example, from waste incineration. PCE is a solvent commonly used in industry and in dry cleaning, leading to both worker and consumer exposures.

Studies of breast cancer and tobacco smoke, including active smoking or passive exposure to environmental smoke from spouses or co-workers or in commercial and leisure settings, are more numerous than for other environmental pollutants, in part because exposure can be easily and inexpensively measured in interviews. Many early studies found no increased risk among smokers, and a recent meta-analysis of 53 studies comparing "ever" to "never" smokers found no association with breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer et al. 2002). However, recent studies that separate active from passive exposure, consider a woman's age at exposure, and take into account genetic polymorphisms that affect the mechanism for ridding the body of smoke provide some evidence for an association, although the data are still inconsistent (Band et al. 2002; Bartsch et al. 2000; Dunning et al. 1999; Kropp and Chang-Claude 2002; Perera 2000).

In general, studies of genetic polymorphisms and breast cancer have focused on genes related to PAH and steroid metabolism (e.g., *CYP*, *GST*, *NAT2*), and studies of interaction between genetic polymorphisms and environmental pollutants have focused on tobacco smoke, with two studies of PCBs. Overall, results of these studies have been inconsistent (Bartsch et al. 2000; Basham et al. 2001; Dunning et al. 1999), with some evidence of effects of *CYP*, *GST*, and *NAT2* polymorphisms and smoking on breast cancer risk, particularly in subgroup analyses (Ambrosone et al. 1996; Bartsch et al. 2000; Chang-Claude et al. 2002; Firozi et al. 2002; Hunter et al. 1997; Morabia et al. 2000; Zheng W et al. 2002; Zheng T et al. 2002, 2003), and two positive reports for PCBs and *CYP* polymorphisms in postmenopausal women (Laden et al. 2002; Moysich et al. 1999).

Overall, the population-based studies of breast cancer and environment represent a very sparse literature. Particularly notable is the focus on smoking and a small number of persistent OCs. Even for the most-studied chemicals, the number of studies is relatively small. In comparison, the recent meta-analyses of pharmaceutical estrogens and breast cancer are based on nearly twice as many studies as have been reported for DDT/DDE.

Challenges and Priorities

A variety of challenges in conducting studies about breast cancer and the environment may have discouraged work in this area, and these challenges define areas where future study will likely have the greatest impact. In particular, lack of exposure assessment tools and lack of toxicologic studies to develop hypotheses limit the scope of epidemiologic studies. In addition, issues of timing with respect to latency and periods of breast vulnerability, and individual differences in genetic susceptibility are challenges in research design that require attention. A substantial investment is needed in basic areas that are the foundation of successful human research—exposure assessment, toxicology, and susceptibility—before we can expect a pay-off from large epidemiologic studies of breast cancer and environment.

Exposure assessment. Multiple aspects of exposure assessment present methodological challenges. As in other cancer studies, latency means that exposures must be assessed for a time period long before diagnosis. For breast cancer specifically, evidence from both animal and epidemiologic studies suggests that there may be vulnerable periods, perhaps during gestation or adolescence or between menarche and birth of a first child, when exposure is most important. In addition, effects of environmental exposures may differ before and after menopause, as seen with some previously studied risk factors (e.g., body mass index and a recent report on smoking; Band et al. 2002). These multiple timing considerations are a particular challenge in studying exposures, such as air and water pollutants, that women cannot report retrospectively, in contrast with exposures, for example, childbearing history, that comprise the recognized risk factors. As yet, none of the available biomarkers can assess exposure dating back many years, let alone decades, and it is a particular challenge to characterize exposures for specific periods of the life span (e.g., during puberty). The complexity of mixtures in both occupational and community settings is another difficulty, along with simultaneous exposure to poorly understood degradation products and metabolites of pollutants.

Recent studies include efforts to improve exposure assessment in light of these challenges. Thus, the Long Island study and new research on tobacco smoke have included a relatively novel measure of PAH–DNA adducts. The Cape Cod Breast Cancer and Environment Study, now under way, defined development of new exposure assessment methods as a core goal (Brody et al. 1996). The study developed a geographic information system (GIS), a computer-mapping database, designed first to generate hypotheses and conduct ecologic analyses and later to assess exposures to wide-area pesticide use and drinking water contamination at individual addresses of 2,100 women in a case–control study (Brody et al. 2002). GIS is also being used in exposure reconstruction in several other epidemiologic studies (Beyea and Hatch 1999; Lynberg et al. 2001; Stellman et al. 2003; Ward et al. 2000). Capitalizing on geographically based research makes sense in studies of pollutants because many exposures vary geographically in relation to sources. Examples of nationally available data include the Toxics Release

Inventory (http://www.epa.gov/tri), which documents point sources of pollutants, and records generated under the Safe Drinking Water Act (1974) for every public drinking water supply (Caldwell et al. 1998). Although some exposure data are available nationally, developing additional GIS exposure data is often more practical in a geographically limited area.

Because of enormous gaps in previous research about breast cancer and environmental pollutants, beginning with a lack of basic knowledge about the frequency and level of exposure to compounds identified as hormonally active or as animal mammary carcinogens, exposure studies that investigate these questions without yet tackling the link to breast cancer are an efficient way to proceed. For example, the Cape Cod Study developed an environmental sampling program for hormonally active compounds and mammary carcinogens in groundwater and drinking water, household air and dust, and women's urine. Results documented a potential pathway of exposure to endocrine disruptors that travel from septic systems to groundwater and drinking water, and identified 72 different hormonally active target compounds in homes, showing substantial opportunity for exposure (Rudel et al. 1998, 2001, 2002). Compounds for which frequent or high exposures have been identified and methods for measuring exposures developed might then be targeted in toxicologic and epidemiologic studies.

Considering that the ideal exposure assessment would provide information about the agent, dose, exposure pathway, timing in relation to latency, and timing in relation to lifecycle development, no one measurement technique is likely to provide a "gold standard." Self-report is vulnerable to response bias and cannot assess pollutant exposures unknown to the study participant. GIS offers a new approach to historical exposures and is independent of knowledge or bias among study participants, but it is vulnerable to missing data and faulty models of relationships between indicators and individual exposures. Environmental and biological sampling methods also may not accurately reconstruct individual historical exposure. Further, measurement methods have been developed for only a limited range of compounds, and measurements are expensive and sometimes intrusive to collect, resulting in small sample sizes with low statistical power and possible bias from nonparticipation. Analyses of relationships among environmental, biological, self-report, and GIS measures can help inform interpretation of studies using each of these exposure assessment methods and help identify sources of exposure. Studies to characterize environmental and biological exposures can also help identify populations or settings with high exposures that may provide unique opportunities for study.

Toxicology and mammary gland biology. Among 70,000 chemicals in commerce, fewer than 1,000 have been tested in cancer bioassays, and there has been no systematic testing for hormonal activity (U.S. EPA 1999). The challenge of analyzing mixtures and the idiosyncratic dose–response relationships (e.g., U-shaped) for hormones and hormonally active pollutants adds another layer of complexity. In addition, the biological and hormonal regulation of mammary gland development and carcinogenesis is poorly understood, so forming hypotheses about how chemicals will affect these processes is difficult.

Although standard animal bioassays for identifying carcinogens provide important direction for study in humans, improvements are needed in the development and application of animal models for mammary tumors specifically. For example, current protocols may not adequately address increased susceptibility to carcinogens for early-life exposures because dosing typically begins in pubertal animals (Bennett and Davis 2002). In addition, the rodent strains typically used for carcinogenesis bioassays may not be optimal for identifying mammary carcinogens, either because of a reduced susceptibility to such tumors ($B6C3F_1$ mice), because a high background rate of mammary tumors makes results difficult to interpret (Fischer 344 rats), or because hormonal regulation of the rodent mammary gland differs from that in humans (Bennett and Davis 2002; Dunnick et al. 1995; Snedeker 2001).

Another important issue for animal models is that, although it is important to identify chemical carcinogens that are genotoxic, which the current protocols are designed to do, it may also be important to identify chemicals that effectively promote the growth of cells after they have been initiated by some other carcinogen. The powerful role of endogenous hormones in promoting breast tumor development suggests that environmental chemicals that act as promoters could play an important role in breast cancer. Assays to look for tumor-promoting activity involve treating with a single dose of an initiator and then following with the promoter. In an assay like this, DDT was found to accelerate the rate of mammary tumor formation in male rats (females were not tested), suggesting that it could be active as a tumor promoter (Scribner and Mottet 1981), and wheat bran was shown to decrease the incidence of DMBA-initiated mammary tumors (Zile et al. 1998). Finally, it is also a priority to develop animal models that characterize the effects of *in utero* chemical exposures on development and susceptibility of the mammary gland in the offspring because *in utero* hormonal environments have been shown to affect later susceptibility to carcinogens (Hilakivi-Clarke et al. 2001).

Individual susceptibility and intermediate outcomes. Consideration of individual susceptibility is another area where limitations in previous research have led to recent innovation. Although high-risk breast cancer genes account for a small fraction of cases, lower risk, more common genetic polymorphisms that affect metabolism of endogenous estrogen and other chemicals are promising directions for study, as discussed above. However, studies to date have yielded conflicting results, in part because of the need for large sample sizes to achieve adequate statistical power and because of limited information on specific functional outcomes of the polymorphisms in relation to mechanisms of breast carcinogenesis (Dunning et al. 1999; Friedberg 2001; Perera 2000; Pharoah et al. 2002). This is another aspect of basic biology that could advance our ability to study breast cancer.

The difficulties of linking exposures with disease may also be remedied by studies of intermediate outcomes and of interactions or effect modification associated with recognized breast cancer risk factors. Studies of effects of chemical exposures on puberty, breast density, and *in situ* disease—all recognized risk factors for breast cancer—reduce the time lag between exposure and outcome measurement. Research to identify new intermediate outcomes, such as hallmarks of mammary gland development, will add to tools available for addressing breast cancer etiology.

Conclusion

Although journalistic reports have recently implied that scientific evidence shows that environmental pollutants are unrelated to breast cancer (Associated Press 2002; Kolata 2002), a review of research in this area reveals a much different picture of major knowledge gaps, difficult challenges in research design, and contrasting bodies of evidence from toxicologic and epidemiologic studies. Strong toxicologic evidence points to a large number of ubiquitous pollutants that are plausibly linked to breast cancer because they mimic or disrupt hormones known to affect breast cancer risk, initiate mammary tumors in animals, or permanently alter breast development, affecting susceptibility. Epidemiologic research is far more limited because very few of the compounds identified as endocrine disruptors or animal mammary carcinogens have ever been targeted in a human breast cancer study. A small but interesting body of occupational studies that link higher risk with jobs involving likely exposures to organic solvents and PAHs is generally consistent with animal studies. The relatively few population-based

epidemiologic studies have been mostly negative overall, with positive results often limited to subgroups. Many plausible reasons for null epidemiologic results have been advanced in this article and elsewhere, including poor historical exposure measurement, restriction to a small number of pollutants, failure to study compounds in current use, low statistical power to detect modest effects, and failure to take into account genetic susceptibility or life-cycle effects. Limited study of women in occupational settings where exposures are relatively high and well defined is another barrier to understanding chemical risks. Given the modest relative risks associated with the recognized breast cancer risk factors, an integrated research agenda for study of environmental pollutants in both laboratory and human settings has great potential. Even if the relative risks of environmental factors are modest, discovery of a risk that can be modified would save many thousands of lives.

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