ANNUAL REVIEWS

Annual Review of Public Health

Environmental Determinants of Breast Cancer

Robert A. Hiatt[1] and Julia Green Brody[2]

[1]Department of Epidemiology and Biostatistics and Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California 94158, USA; email: robert.hiatt@ucsf.edu

[2]Silent Spring Institute, Newton, Massachusetts 02460, USA; email: brody@silentspring.org

Annu. Rev. Public Health 2018. 39:113–33

First published as a Review in Advance on January 12, 2018

The *Annual Review of Public Health* is online at publhealth.annualreviews.org

https://doi.org/10.1146/annurev-publhealth-040617-014101

Keywords

epidemiology, toxicology, chemical toxicants, social determinants, endocrine, disrupting chemicals

Abstract

In the United States, breast cancer is the most common invasive malignancy and the second most common cause of death from cancer in women. Reproductive factors, estrogen, and progesterone have major causal roles, but concerns about other potential causes in the external environment continue to drive research inquiries and stimulate calls for action at the policy level. The environment is defined as anything that is not genetic and includes social, built, and chemical toxicant aspects. This review covers the scope of known and suspected environmental factors that have been associated with breast cancer and illustrates how epidemiology, toxicology, and mechanistic studies work together to create the full picture of environmental effects on this malignancy. Newer approaches to risk-related evaluations may allow this field to move forward and more clearly delineate actionable environmental causes of this most common of cancers in women.

INTRODUCTION

The etiology of breast cancer is complex. There is not one cause of breast cancer but many (53). There is not one type of breast cancer but several (69). Breast cancer has a great impact on population health as the most common invasive malignancy and the second most common cause of death from cancer in women. Additionally, it strikes women while they are in their most productive years, and because of myriad influences on the quality of life and impact on families, breast cancer has a huge impact on women's overall health and deserves the scientific attention it gets.

Since the early 1990s, there has been a downward trend in mortality; in the period 2010–2014, this trend decreased annually at an average of 1.6%, whereas in the same period incidence increased slightly at an average of 0.3% per year (65). Incidence has increased in all race/ethnic groups except whites, which could be due to increased screening or to real increases in new cancers; thus, the meaning of this increase could be either positive or negative.

Sorting out the multiple factors responsible for causation of breast cancer has occupied scientists for decades. The well-known almost fivefold difference in breast cancer incidence across countries internationally is unlikely to be due to genetic predisposition and points to environmental factors or living conditions in high-income countries (40, 90). The observation that immigrants from low-incidence countries experience the higher incidence rates of countries to which they migrate illustrates that whichever environmental factors are in play can act to increase rates in genetically similar people in two generations (162). Within the United States, rates vary substantially (133), and certain communities and areas of the country with the highest incidence rates have seen elevated public concern and advocacy generated to better understand the problem and act to reduce excess risk (14, 42, 52, 89). Reproductive factors clearly play a major role related to exposure to cyclic estrogen and progesterone (67), but concerns about other causal factors, especially from external environmental sources such as chemical toxicants, continue to drive research inquiries and stimulate calls for action at the policy level (116).

SOURCES OF EVIDENCE

Methodologically, it can be difficult to establish a causal relationship between environmental chemical exposures and breast cancer. Most studies in adult women rely on the recall of self-reported exposures earlier in life or on levels of putative chemicals in biospecimens often collected after the time of diagnosis. However, people often do not even know they were exposed to particular chemicals. Recalled product use or geographic location may not be sufficiently detailed or accurate. When assays of chemicals are performed after diagnosis, residues may not represent exposure at the relevant time in life, thus impeding the ability to establish causality.

The recognition that human epidemiologic studies in the real world have these limitations has led to the realization that evidence from many sources is needed. The assessment of cumulative risk requires different tools and more types of evidence in order to make good and defensible decisions for environmental health interventions and policies. Many scientific disciplines are engaged in solving this challenge, including genetics, molecular biology, toxicology, endocrinology, epidemiology, and others (81).

This review describes the scope of what is known about the environment and breast cancer. For additional detail, we refer the reader to two major reviews of environmental effects on breast cancer: one from the Institute of Medicine (now the National Academy of Medicine) in 2012 (64) and the other from the Interagency Breast Cancer and Environmental Research Coordinating Committee in 2013 (63). A recent report on the recommendations of an expert panel on the

effects of endocrine-disrupting chemical (EDC) adds an additional perspective (135) as does a recent update of a comprehensive review of environmental chemicals and breast cancer (116).

DEFINITION OF ENVIRONMENT

A broad definition of environment includes anything that is not genetic (64). The environment can in turn be divided into the sociocultural environment, the built environment, and the toxicological or chemical environment. Various attempts have been made to determine how much of breast cancer incidence can be explained from known or highly suspected risk factors such as ages of menarche, menopause, and first full-term pregnancy (82) or from occupational exposures (111). However, the determination of population attributable risk (PAR), which is the percentage of excess cases that can be associated with an exposure of interest, is difficult to determine for known risk factors and breast cancer (64).

Social Environment

Breast cancer risk is elevated among women of higher socioeconomic status (SES) perhaps owing largely to reproductive patterns (80, 115). Areal measures of SES have also been associated with increased risk. Neighborhood SES based on social and built environment characteristics has been associated with a twofold greater risk for women living in the highest quintile of neighborhood SES risk versus the lowest for all major race/ethnic groups (27).

Factors related to the early-life socioeconomic environment are difficult to study because of the lack of longitudinal data across the life course and meaningful biomarkers of intermediate outcomes. To date, studies of early-life SES and adult breast cancer incidence and mortality have been inconsistent (31, 96, 110, 132, 137). Other effects of the social environment might be manifest through family structures. It has been intriguing to note that in families where the biologic father is absent for whatever reason, some studies show that girls go through puberty earlier (32), thus potentially increasing their risk of breast cancer.

Built Environment

The built environment is that which can be attributed to people's purposeful activities to construct and influence the physical world. Where people live, work, and play may act in positive ways to provide fresh food outlets or open space for recreation, walking paths, and other elements that may stimulate physical activity. Likewise, the built environment can act in negative ways, such as when toxic dumps are located next to where people live, when corner stores provide easy access to alcohol and tobacco products, and when the lack of sidewalks and other features inhibit walking and other forms of physical activity.

The social and built environment attributes of neighborhoods seem to play a role in breast cancer risk, and considering these influences across diverse populations may be key to understanding related racial/ethnic inequities in breast cancer risk (28). There is also evidence that multiethnic neighborhoods with composite characteristics associated with lower SES based on education, housing, employment, income, and the built environment (e.g., recreational facilities, unhealthy retail and restaurant options) are more obesogenic and associated with breast cancer risk (27). Physical activity, which has generally been associated with contact with green spaces where people live (140), has been inversely associated with breast cancer incidence (41, 155). The food and retail environment of a neighborhood may be related to total energy intake in young girls (76) and negatively influence their development.

Toxicologic and Chemical Environment

In recent decades, the evidence from toxicologic and mechanistic studies relevant to breast cancer etiology has substantially increased (118, 119). Studies have attempted to assess associations between exposures to environmental chemicals and either breast cancer or some intermediate outcome relevant to breast cancer (e.g., age at menarche). A thorough review of epidemiological studies of environmental pollutants and breast cancer was published by Brody et al. (12).

SPECIFIC ENVIRONMENTAL EXPOSURES

We have grouped environmental exposures into lifestyle factors or exposures influenced by human choices and behaviors, endocrine disrupting chemicals, primarily in personal products, and industrial and agricultural chemicals. The first group of behavioral factors are influenced not only by personal choices, but also by societal and environmental circumstances beyond individual control.

Exogenous Hormones

Hormone replacement and oral contraceptives. Breast cancer is a hormonally dependent malignancy, and the relationship of oral contraceptives and hormone replacement therapy to breast cancer has thus been of great interest to researchers over the years. Oral contraceptives are used for birth control and other medical reasons by about 16% of females aged 15–44 years (30). Evidence indicates that they are carcinogenic for current users, but the risk dissipates after 4 years when stopped (56). Because most use of oral contraceptives is among young women in their reproductive years when the risk of breast cancer is low, the risk of breast cancer from oral contraceptives at the population level is low.

Use of combined estrogen–progestin hormone therapy (HT) at menopause was a common practice until the results of the Women's Health Initiative showed an increased risk of breast cancer that was not offset by other health benefits (e.g., to cardiovascular disease) in these women (4). The prevalence of HT use subsequently dropped markedly in the United States, and declines in breast cancer rates soon followed (35). As with oral contraceptives, risk is associated with current use and diminishes within several years when stopped (7). Recommendations for HT use for menopausal symptoms are now made much more cautiously.

Diethylstilbestrol. Diethylstilbestrol (DES) exposure was first introduced in 1938 to prevent miscarriages and was in use until 1971. This estrogenic compound was taken off the market when it was discovered that daughters of women who took it during pregnancy developed adenocarcinomas of the vagina (49). Subsequently, as the women who took DES have aged, multiple reproductive abnormalities have emerged, including increased breast cancer rates (105, 138). Breast cancer rates have been elevated, especially for cancers occurring in individuals $\geq$50 years of age [relative risk (RR) 3.0, 95% confidence interval (CI), 1.01–8.98] (105). We have learned that in utero exposures can have important and devastating effects on adult health many years later and that the period of organogenesis during fetal life is one of several periods of life (windows of susceptibility) when humans are sensitive to the effects of carcinogens, in this case synthetic estrogens.

Obesity

Obesity has multiple determinants among which are factors associated with the built environment (26, 28, 140). Obesity as measured by body mass index (BMI) has long been known to be associated

with an elevated risk of postmenopausal breast cancer, a decreased risk of premenopausal breast cancer, and an earlier age at menarche (154). However, BMI may not be the critical measure of body fatness; rather, abdominal fat, which is thought to be more biologically important in terms of insulin resistance and cancer risk, may be more critical. The paradoxical relationship of obesity in pre- versus postmenopausal women may be due to the differential frequency of estrogen receptor positive/progestin receptor positive (ER+/PR+) tumors in these two age groups (160). ER+/PR+ tumors are more common postmenopausally and more sensitive to estrogen, which is produced by fat tissue at that stage of life. ER−/PR− tumors are more common premenopausally and may have a different relationship with traditional risk factors because these tumor types represent different aspects of the disease. Fat tissue may also act as a storage medium for EDCs (see below) that are lipophilic and reside in the body for long periods of time (147) and may themselves act as obesogens (8). More work needs to be done to sort out the reasons for the life course variability in the relationship between obesity and breast cancer.

Physical Activity

Physical activity is another external environmental factor that is modifiable in favor of breast cancer prevention. Most epidemiologic studies have found a protective effect of physical activity, no matter the type, but it is probably only for postmenopausal breast cancer. The evidence for a protective relationship between physical activity and premenopausal breast cancer risk is less consistent (154). The mechanism probably works through reducing the level of body fatness but may also work through reducing estrogen levels (154). A more complete understanding of the interactions among environmental pollutants, physical activity, diet, and breast cancer would offer more opportunities for prevention (13).

Dietary Factors

Several decades ago, much research was done to evaluate dietary fat and other major nutrients as causal features for breast cancer because such a theory was so consistent with the fivefold international variation in breast cancer rates. However, that line of research failed to demonstrate a clear relationship with breast cancer (144). Rather high energy intake and low physical activity leading to prepubertal obesity and associated weight gain in midlife may explain the large international differences in breast cancer incidence associated with fat intake. Some evidence suggests that monounsaturated fats (e.g., olive oil) may actually reduce the risk of breast cancer (144).

Alcohol. Alcohol consumption as a causal factor in breast cancer has been well documented from more than 100 studies using both case-control and cohort designs and from multiple countries around the world (64). Overall, the magnitude of the relative risk is about 1.5 for the consumption of 45 g of alcohol per day (26), which is equivalent to about 3 alcoholic drinks per day and holds for any type of alcohol (wine, beer, or spirits) (154). Data are inconsistent on whether there is a particular time of life when alcohol consumption puts women at higher risk compared with other times of life. However, it does appear that alcohol consumption has more of an effect on ER+/PR+ tumors and not for ER−/PR− malignancies (134). Animal studies have confirmed this finding; rodents exposed to alcohol have increased tumorigenesis in most studies (104). The mode of action is unclear and alcohol could act through the formation of genotoxins such as acetaldehyde or through the alteration of hormones, hormone receptors, or other mechanisms (64, 104).

Phytoestrogens. Epidemiologic studies on the effects of phytoestrogens on breast cancer have been mixed but tend toward being protective if consumed in sufficiently high doses (107). Soy intake is substantially higher among some Asian populations than among those in North America, and because dose is a critical factor, discussion of epidemiologic results for phytoestrogens needs to take into account the population studied. Several well-conducted studies, mostly using case-control designs in Asia where intake of soy products is high, have tended to show a protective effect (156). A meta-analysis of eight studies in Asian countries showed a significant trend whereby risk decreased with increasing soy intake. In contrast, 11 studies in Western countries showed no protective effect.

Well-conducted epidemiologic studies of adolescent soy intake are fairly consistent in showing a graded protective effect with dose (71, 75, 125, 158). Finally, in young girls, in a cross-sectional study of 192 healthy 9-year-olds in New York, lower urinary phytoestrogen levels were associated with earlier breast development (148).

Vitamin D. In recent years, there has been much interest in the role of vitamin D in breast cancer incidence as well as survival and mortality. Vitamin D can be measured by sun exposure estimates, dietary intake, and circulating serum 25(OH)D. Although current evidence is lacking on the possible protective effects of vitamin D in early development (126), there is no evidence of any protective effect of vitamin D supplementation on breast cancer etiology. In the Women's Health Initiative trial in 36,282 women, 25 (OH)D (400 IU D3 per day) given with supplemental calcium showed no effect on lowering breast cancer incidence (21).

Tobacco

Tobacco smoke contains more than 20 components that are known carcinogens (59), and these substances can be found in the breast fluid and tissue of women who smoke (92, 139). Recent reviews of existing epidemiologic literature by the International Agency for Research on Cancer (IARC) and a Canadian review group support a causal relationship between active smoking and breast cancer, especially in women who initiated smoking before their first full-term pregnancy and among women who have a genetic trait, NAT2 slow acetylators, that slows the metabolism and detoxification of tobacco carcinogens (66, 122).

Exposure to secondhand or environmental tobacco smoke (ETS) has also been associated with increased risk of breast cancer in never smokers, although the conclusions about causality vary by different agencies. The IARC has found the evidence to be inconclusive, whereas the California Environmental Protection Agency and the Canadian review judged the evidence to be consistent with causality in younger, premenopausal women (66, 91). Evidence from the California Teacher's Study supports an increased risk in postmenopausal women as well (113).

ETS has been assessed in girls and associated with early menarche (114, 145). However, mechanisms by which ETS might contribute to earlier menarche remain to be elucidated, especially by examining possible gene–environment interactions such as those with N-acetyltransferase 2 (NAT2) slow acetylator and glutathione S-transferase Theta 1 (GSTM1) null genotypes, which may be associated with breast cancer in adults (1, 136).

Radiation

Ionizing radiation is an environmental exposure for which there is clear and very strong evidence of carcinogenicity for breast cancer. Evidence from survivors of the atomic bomb explosions in Japan has documented the sensitivity of these individuals to radiation of the developing breast

(20). The most important source of exposure from ionizing radiation is now from diagnostic medical imaging, including radiographs, fluoroscopy, and computed tomography (64). Efforts to standardize and regulate the application of medical diagnostic radiation should result in substantial reductions in the risk associated with this environmental exposure (127).

Light at Night

Exposure to light at night, which often is the same as shift work, has been repeatedly associated with increased breast cancer rates (70), and the IARC has classified shift work as probably carcinogenic for breast cancer (61). The mechanism is unclear but could work through the suppression of melatonin, which normally rises during the darkness of night and is antiestrogenic (47). These findings are of concern because many nighttime shift workers are women in the health care and service industries (61). Work on the mechanism of this relationship is continuing.

Metals

Metals are ubiquitous in the environment both from natural sources and from industry, transportation, and fossil fuel combustion in general. Some metals, including arsenic, beryllium, cadmium, chromium, nickel, and related compounds, have been judged carcinogenic in humans by the IARC (131). The best-demonstrated evidence for carcinogenicity in humans is for lung cancer. Epidemiologic evidence for an increase in breast cancer risk is limited, perhaps because most of the occupational studies of heavy metals have been done in men. Both lead and cadmium have estrogenic properties (24) and have been associated with breast cancer in human epidemiologic studies (19, 87). Lead exposure has been associated with later pubertal onset or menarche in several studies (34, 123, 157).

Endocrine Disrupting Chemicals—Personal Products

The evidence that endogenous hormones influence breast cancer risk raises parallel questions about the effects of synthetic chemicals that mimic or disrupt hormones, particularly estrogen signaling. Many chemicals currently in widespread use in consumer products have estrogenic activity in rodent models and in vitro. Many of these compounds are rapidly metabolized, complicating exposure assessment for epidemiological studies (116).

Bisphenol A. The widely used industrial monomer bisphenol A (BPA) is a weakly estrogenic chemical that is polymerized in the manufacture of polycarbonate plastic and epoxy resins. Human exposure occurs when BPA is leached from plastic-lined food and beverage cans and many other common sources in modern life (15, 101). Estrogenic effects of BPA (86, 117) and effects on weight gain, puberty, male and female reproductive tract abnormalities, and the mammary gland in animal models have been documented (83).

In humans, urine BPA levels in parts per billion (ng/ml) have been documented in many studies; one large study revealed that 95% of urinary samples tested contained BPA levels in parts per billion (ng/ml) (16) as did 94% of samples tested in a study of prepubertal 6–7-year-old girls in the Breast Cancer and the Environment Research Program (BCERP) across the United States (152). However, researchers are uncertain about the level and risk of exposure to BPA in humans. In one of the few epidemiologic prospective studies of the health effects of BPA in 1,151 girls between 6 and 8 years old, after two years of follow-up, the data showed no statistically significant effect on pubertal onset (151).

Parabens. Parabens are antimicrobial preservatives found in personal care products, including underarm cosmetics, which can act like weak estrogens to bind to the estrogen receptor. Data in humans have documented parabens in urine in almost all (>96%) of a demographically diverse sample of adults (161), and parabens have been documented in breast cancer specimens. Although the levels were previously thought to be lower than that required to produce estrogenic effects (106), they can stimulate breast cancer cell proliferation in vitro at concentrations 100 times lower when in the presence of the growth factor heregulin (106). A recent study measured urine parabens levels in a diverse sample of 1,151 6–8-year-old girls as a possible determinant of pubertal onset two years later and found no relationship. Paraben levels, which often occur together with benzophenome-3 (BP-3), a phenol found in sunscreens, were, however, significantly higher in the summer and among white girls (151).

Phthalates. Personal care products and cosmetics may include phthalates and organic solvents as well as parabens (150). Butyl benzyl phthalate (BBP) is an estrogenic compound and a partial agonist for the estrogen receptor (2). BBP is widely used in food wraps and other plastics as well as in cosmetic formulations. A recent case-control study in northern Mexico compared 233 breast cancer cases to 221 age-matched controls on urinary levels of phthalates obtained (in the cases) prior to treatment. Cases had significantly higher levels of monoethyl phthalate (MEP), but controls had higher levels of other phthalates (78). This finding is provocative because there are no other known epidemiologic studies (54) attempting to relate phthalate exposure to breast cancer. Studies of pubertal timing in 30 Taiwanese girls with premature thelarche (breast development) were compared with 26 girls with central precocious puberty and 33 normal controls; the girls with premature thelarche were found to have higher levels of monomethyl phthalate (MMP) than the control group ($p = 0.005$) (22). Another much larger study, again from the BCERP, has assessed a panel of nine phthalate metabolites. In 1,149 girls analyzed, investigators noted a nonstatistically significant relationship to pubertal onset as measured by either breast or pubic hair development with two years of follow-up associated with low-molecular-weight phthalates and a weakly inverse association relationship for high-molecular-weight phthalates and pubic hair development ($p = 0.04$ for trend in quintiles) (151). Low-molecular-weight phthalates were associated with girls' gain in BMI and waist circumference in this study (33). Overall, evidence seems to suggest that phthalate exposure may be associated with breast cancer and breast cancer risk factors early in development, although the direction of the relationship for different phthalates is inconsistent.

Polybrominated diphenyl ethers. A study of brominated flame retardants [polybrominated biphenyls (PBBs)] among accidentally exposed farmworkers in Michigan revealed an association with earlier pubic hair development but not earlier breast development in the daughters of exposed mothers (9). Epidemiologic studies in adults have not shown any relationship to breast cancer (57). However, serum levels in the BCERP study of polybrominated diphenyl ethers (PBDEs) were detected in 70% of girls from California and Ohio. Levels were higher for girls from California (146), probably owing to California's fire regulations and safety codes (163). Flame retardants with PBDE have been phased out of production but are widely persistent in the environment (36).

Perfluoroalkyl substances. Perfluoroalkyl substances (PFASs) are a family of per- and polyfluorinated chemicals that have also found their way into the environment and have EDC properties. Two of the most widely studied are perfluoroactanoic acid (PFOA) and perfluorooctane sulfate (PFOS) (74). PFOA is a synthetic compound introduced halfway through the last century for use in many industrial and consumer products, including Teflon and Gore-Tex (129). Detectable levels can be found in the serum of most persons tested in the United States (17). In animal

systems, PFOA has been associated with tumor development (119), probably owing to effects on the immune and endocrine systems rather than genotoxicity (129). Epidemiologic studies are very limited, to date, for cancer-relevant outcomes in general and especially for breast cancer (102, 129). The Danish National Birth Cohort found significantly elevated odds of breast cancer among the women in the highest compared with the lowest quintile of perfluorooctanesulfonamide (PFOSA), which breaks down in the body to PFOS, and further follow-up in this study will be informative (10). Other recent studies have been methodologically limited and have found no consistent relationships (102).

Industrial and Agricultural Chemicals

Women are exposed to a range of industrial and agricultural chemicals and their byproducts at work and in community settings. In addition to EDCs, these exposures include chemicals that increase mammary gland tumors in rodent assays (118).

Benzene. Benzene is an industrial chemical that has been classified as a human carcinogen, primarily on the basis of occupational studies in men and hematopoietic cancers (58). A number of epidemiologic studies support its role as a carcinogen in women as well (29, 108), and animal studies in rodents exposed to benzene orally or by inhalation show an increase in mammary tumors (84), perhaps via genotoxic mechanisms (5). Benzene is now regulated as a carcinogen for its causal relationship to hematopoietic cancers, so its use for nonindustrial purposes has been limited. However, it is a combustion product of natural gas and gasoline and remains in the environment at lower levels. Exposure should be minimized to protect against breast cancer (64).

Ethylene oxide. Ethylene oxide is another industrial chemical that is used primarily for medical equipment sterilization procedures, so women working in hospital settings are at risk of exposure. On the basis of animal, mechanistic, and limited epidemiologic data, the IARC classified ethylene oxide as a carcinogen (60). The strongest epidemiologic study so far in a large occupational cohort found a significantly increased risk of breast cancer of 1.74 (95% CI 1.16–2.65), which remained high after adjustment for parity and family history of breast cancer (130). Together, these epidemiologic data along with the animal and mechanistic studies support the likelihood that ethylene oxide can work as a carcinogen in adults (64).

1,3-Butadiene. 1,3-butadiene is a gas also found in petroleum products and cigarette smoke and, like benzene, is classified as a carcinogen on the basis of occupational studies linking it to hematopoietic cancers (6). Although there are no studies of its effects on breast cancer in women, studies in rodents, again like those for benzene, show higher rates of mammary tumors and evidence of genotoxic damage (60). It is unlikely that any studies of 1,3-butadiene in women will be mounted because the use of and exposure to this chemical are already limited. It would also be difficult to find enough exposed women to achieve any meaningful epidemiologic data (64).

Polychlorinated biphenyls. Polychlorinated biphenyls (PCBs) are a family of 209 organochlorine congeners that were used as industrial coolants, insulators, and lubricants as well as for many other applications until the United States banned their use in 1979. Decreasing human body burden concentrations have been documented over the past 20 years. PCBs have been inconsistently related to breast cancer in epidemiologic studies, including agricultural exposures in cohort studies (37). Evidence from at least four studies demonstrates a gene–environment interaction with CYP1A1 such that high levels of PCB exposure and expression of CYP1A1 confer a higher

risk of breast cancer (12, 24, 73, 95). Because individual congeners have different, and sometimes opposing, biological effects, epidemiologic studies face challenges in defining meaningful congener groupings for analysis (149). In a study that measured serum PCB levels in early postpartum women in 1959 to 1967 (a period of peak PCB use), women with a higher proportion of PCB 203 in relation to the sum of PCBs 167 and 187 were more likely to be diagnosed with breast cancer by age 50 (24).

Pesticides

Epidemiologic studies of organochlorines and breast cancer have included both DDT and PCBs, but most have focused on exposure to the pesticide p,p′-DDT and its metabolite p,p′-DDE. Various study designs have compared adult women with breast cancer to women without. Despite the large number of studies in this area following the initial positive results in case-control studies (38, 153), the results are mostly negative and do not support the hypothesis that residues of organochlorines in adults are associated with increased breast cancer risk (18, 79).

Then, in 2007 Cohn and colleagues reported a study using stored sera collected from women in the Child Health and Development Studies at the time of childbirth (average age 26 years), 129 of whom went on to develop breast cancer before 50 years of age (i.e., premenopausal) (25). Compared with 129 women from the same cohort who did not develop breast cancer, those who were in the highest tertile of p,p′-DDT exposure were 2.8 times (95% CI 1.2–6.7) as likely to develop breast cancer as were those in the lowest tertile. The strongest relationship was seen in women who were <14 years in 1945 [odds ratio (OR) = 5.4, 95% CI 1.7–17.1]. This study, which cannot be replicated because of the unusual nature of the data set, supports the concept that the timing of exposure (i.e., early development window) may be critical to the contribution of EDCs to carcinogenesis (23). Supportive evidence comes from the Sister Study, which found that young girls up to age 18 years who were exposed to fogger truck or plane spraying of DDT were at a nonsignificant increased risk of breast cancer [hazard ratio (HR) = 1.3, 95% CI: 0.92–1.7] for premenopausal breast cancer (100). Similarly, the Long Island Breast Cancer Study Project reported increased odds of ER+/PR+ breast cancer among women who reported chasing after a fogger truck in their youth (143).

Organochlorines as a class are lipophilic and resistant to degradation. They were banned from use in the 1970s and 1980s because of toxicities. Nevertheless, organochlorines are still ubiquitous in the environment and can be measured in biospecimens from virtually all US adults and children. Traditional epidemiologic observational studies in adulthood of the association between organochlorines and breast cancer have been inconsistent, however (120, 159). Some cohort studies have found associations with one organochlorine, for example dieldrin, but not others (55). Even in studies of large populations who were logically at very high risk of exposure during adulthood, such as farmer's wives in the Agricultural Health Study, no clear relationships between overall pesticide exposure and breast cancer were established. Associations with earlier menarche have been positive in several (45, 103, 141) but not all studies (34).

Air Pollution and Polycyclic Aromatic Hydrocarbons

Air pollution is a designated human carcinogen on the basis of mechanistic, animal, and epidemiologic evidence (62). Individual constituents of air pollution include genotoxins and estrogenic and antiestrogenic compounds. The most studied of these are polycyclic aromatic hydrocarbons (PAHs), which have been linked to breast cancer in animal models and epidemiologic studies (116). PAHs are a large class of chemicals formed by the incomplete combustion of coal, oil, and

gas, as well as grilled meats, tobacco smoke, and other substances to which humans are exposed in ambient air and diet. These substances are genotoxic and known to be potential breast carcinogens (94), perhaps by damaging DNA through oxidative stress. Some PAHs are also weakly estrogenic, thus presenting another mechanism by which they may influence breast cancer etiology (121). Because air pollution can vary by neighborhood environments, there may be an interaction between PAH exposure and the social environment, with more disadvantaged neighborhoods at greatest risk (93).

Air pollution, assessed by modeling exposures at residential locations, has become an active area of breast cancer research. The largest study, the ESCAPE Project in 15 European cohorts of postmenopausal women, found significantly higher breast cancer risk associated with nitrogen oxides (NO*x*), a marker for traffic pollution, and nickel, a marker for heavy oil combustion and industry (3). The study found suggestive associations for NO_2, and the US Sister Study found significantly higher risk of ER+/PR+ tumors with NO_2 exposure (112). The California Teachers Study found associations between ER+/PR+ tumors and some mammary gland carcinogens (44) and between ER−/PR− tumors and ambient benzene (44), cadmium, and arsenic (77). The Nurses' Health Study II did not find these associations (48), but the cohort was younger than that of the California Teachers Study. Additional studies with suggestive and null findings were reviewed by in Rodgers et al. (116). Lack of consistent findings may be due to differences in follow-up periods, measurement error from modeled exposure limited to residences, lack of exposure data from early life, and lack of differentiation of pre- and postmenopausal disease and tumor types (116).

Studies in occupational settings, residential studies with earlier life data, and measurements of PAHs add evidence of associations between breast cancer and air pollutants. In western New York, exposure to both benzene and PAHs was assessed from occupational histories that aimed to determine the probability and intensity of exposures in different job classifications. Data from the histories revealed a 2.3-fold elevated risk of ER+ (but not ER−) breast cancer cases compared with women matched by age and county of residence (109). In another study from western New York, women with higher estimated exposure to total suspended particulates (TSP) at their birth residence had higher breast cancer risk later on; TSP levels were associated with a 2.4-fold elevated risk that was on the borderline of significance (11). A more recent study from the same group studied exposure to traffic emissions among women with breast cancer; residence served as an indirect measure of exposure. The study determined exposures at various points in the life course, including the age of menarche. In this study, elevated risk, again slightly over twofold, was observed for exposures at the time of menarche and age at first birth for women with postmenopausal breast cancer (99). A study from the longitudinal BCERP found an association of andrenarche with living in proximity (within 150 m downwind) of traffic-related air pollution (88). A recent nested case-control study with 80 cases and 156 controls found that women with detectable PAH levels had a twofold increase in breast cancer risk compared with women without detectable levels, and there was a dose–response relationship with women with higher levels of PAH exposure having more than a fourfold increase in risk (124). A study of women workers in Canada (72) found that elevated risk of breast cancer was associated with longer employment in jobs associated with vehicle exhaust, especially if exposure began when they were younger than 36 years.

The Long Island Breast Cancer Study has observed higher breast cancer risk associated with PAH–DNA adducts and explored interactions with more than a dozen gene variants (116). Higher breast cancer risk has been observed particularly for higher levels of adducts in women with variants related to poor cell repair (116). Although the studies from western New York have been rather consistent in their levels of risk estimates and the studies from the Long Island Breast Cancer Study have linked PAH–DNA adducts to breast cancer, the role of PAHs in breast cancer etiology in humans is still being actively pursued (43).

Dioxin

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is also an organochlorine, but one that is a product of combustion, metal processing, and chemical manufacturing. It is one of the most toxic substances known and, like DDT and PCBs, is persistent in the environment. Effects on human health have included concerns for cancer and more general reproductive and endocrine effects (68). Easily identifiable exposures to this compound have largely taken place in occupational settings and accidents, so large-scale epidemiologic studies have not been feasible to organize. Rather, most human data on the impact of TCDD comes from occupational health cohorts in which doses are higher than in the general environment and the number of women is proportionally small (85). The EPA considers TCDD "carcinogenic to humans" for all cancers together and for lung cancer, there being little data specific to breast cancer.

Evidence of another sort comes from the Seveso Accident in Italy in 1976, during which a large population surrounding a chemical plant was exposed to TCDD. Twenty-year follow-up of cancer incidence in 111,874 women with graded exposures to dioxin has resulted in no elevations overall; however, after 15 years of follow-up, 5 cases occurred, which is significantly more than expected (RR 2.57: 95% CI 1.07–6.20) (108). After 32 years of follow-up, 33 breast cancer cases had occurred, and the risk was increased for women with higher blood levels of TCDD with 0–10 years and 11–20 years but not 21–32 years of follow-up; this finding suggested a possible window effect (142). Longer follow-up may reveal more cases and clearer relationships to the exposure.

SYNTHESIS

As we indicated at the beginning of this review, breast cancer is complex. The multitude of environmental factors to consider let alone the ever-expanding understanding of genetic variants, gene–environment interactions, and tumor characteristics makes it difficult to grasp the full picture of how the external environment plays a causal role in breast cancer incidence and mortality. Even attempts to model the complex factors involved in breast cancer etiology have to, by necessity, leave out the full scope of factors known or suspected to be involved in the origins of this cancer (53). In addition, for epidemiologic studies, there are multiple methodologic challenges to the investigation of environmental factors and breast cancer (51). Exposures of interest likely occur early in life, even in utero, and are thus difficult to recall in adult life. Longitudinal studies, which would be ideal theoretically, have to be continued for multiple decades to observe breast cancer outcomes from these early exposures. Case-control studies, which can be conducted in less time, suffer from recall bias when exposures are self-reported. In any epidemiologic study, the exposures at different points along the life course may be difficult to assess because of participant mobility across varying geographies and occupations. Biomarker measurements are helpful if available but not if the chemical is not persistent in human tissues (51).

We have reviewed many, but not all, of the nongenetic factors and agents thought to be important nongenetic causes in breast cancer. For the most part, this and other reviews (63, 64, 135) have presented environmental factors independently (e.g., phthalates, benzene). However, in the real world, these factors interact and are dynamic over time. Chemical toxicants frequently present in mixtures, as is the case, for example, with cosmetics and endocrine disruptors. Furthermore, although we have incorporated evidence about the timing of exposures in some cases, a more systematic approach is needed to understand exposures throughout the life course and the concept of "windows of susceptibility" (39, 46). The breast is the only organ that develops and matures after birth, and the dynamic states of proliferation and involution that accompany pubertal onset, pregnancies, and menopause all offer opportunities to better understand just when during the life

course a particular environmental factor is likely to have a critical effect. Additional complexity also faces science when one considers the more than 85,000 industrial chemicals and other factors in the environment that have yet to be studied. New approaches will be needed to efficiently evaluate existing and as yet unknown factors that may cause cancer. We can learn from the science that has gotten us this far, but the field needs new methods of inquiry for the twenty-first century.

The National Academy of Science has issued a report called *Using 21st Century Science to Improve Risk-Related Evaluations* (97). The report builds on previous reports (98) to tackle the onslaught of new data being generated from government, industry, and academia, with the goal of "inform[ing] risk assessment and support[ing] decision-making to improve public health and environment" (97, p. 1). The Academy's approach was to assess scientific and technological advances in the four elements of risk assessment: hazard identification, dose–response assessment, exposure assessment, and risk characterization and to add into this mix their evaluation of the increasingly critical role of epidemiology. This challenge clearly requires a transdisciplinary approach to science, involving toxicologists, exposure scientists, epidemiologists, and other scientists from the basic and social sciences (50). Together, observational epidemiologic studies, natural experiments, and novel study designs, along with toxicological and mechanistic studies, are creating a fuller picture of the role of the environment in breast cancer.

In addition, several approaches to assessing cumulative environmental impacts have been recently reviewed and will likely be helpful in advancing the science that pursues the environmental causes of breast cancer. These include health risk assessments, ecologic risk assessment, health impact assessment, biomonitoring, assessments of the burden of disease, and mapping of cumulative impacts (128). Health risk assessments rely not just on epidemiologic studies in humans, but also on controlled exposure studies in humans (97), toxicologic studies in animals, and mechanistic studies (98). Ecologic risk assessment and health impact assessments take into account qualitative data on context to develop a broader picture of environmental impact.

In conclusion, this review has documented many of the factors in the environment that have associations with breast cancer and could be causal. These factors may have direct effects, or they may act indirectly through mediators such as obesity or earlier puberty. We are clearly in an era when complex interactions, upstream causal factors, and multiple pathways of causation must be considered. We can no longer be comfortable with an etiologic model for cancer that simply apportions causal factors (e.g., diet, tobacco, the environment) to a certain percentage slice of the pie.

The application of these studies is primarily in the realm of public policy because individual interventions to avoid known hazards may not be effective and put too much of the burden for action on the individual. The option of testing the risks associated with chemicals and other toxics through experimental trials is unethical. The challenge for science is to use observational epidemiology, exposure science, toxicology, and mechanistic studies to produce the best evidence possible for making wise decisions.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

J. Brody's contributions were supported in part by NIH grant number U01ES026130 and the Cedar Tree Foundation. The authors thank Ms. Kristen Newhouse for her assistance in manuscript production.

LITERATURE CITED

1. Ambrosone CB, Kropp S, Yang J, Yao S, Shields PG, Chang-Claude J. 2008. Cigarette smoking, *N-acetyltransferase 2* genotypes, and breast cancer risk: pooled analysis and meta-analysis. *Cancer Epidemiol. Biomark. Prev.* 17:15–26
2. Andersen HR, Andersson A-M, Arnold SF, Autrup H, Barfoed M, et al. 1999. Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals. *Environ. Health Perspect.* 107(Suppl. 1):89–108
3. Andersen ZJ, Stafoggia M, Weinmayr G, Pedersen M, Galassi C, et al. 2017. Long-term exposure to ambient air pollution and incidence of postmenopausal breast cancer in 15 European cohorts within the ESCAPE project. *Environ. Health Perspect.* 125:107005
4. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, et al. 2004. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 291:1701–12
5. ATSDR (Agency Toxic Subst. Dis. Regist.). 1997. *Toxicological Profile for Benzene*. Atlanta: US Dep. Health Hum. Serv.
6. Baan R, Grosse Y, Straif K, Secretan B, El Ghissassi F, et al. 2009. A review of human carcinogens—Part F: chemical agents and related occupations. *Lancet Oncol.* 10:1143–44
7. Beral V, Reeves G, Bull D, Green J, Million Women Study Collab. 2011. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J. Natl. Cancer Inst.* 103:296–305
8. Biro FM, Greenspan LC, Galvez MP. 2012. Puberty in girls of the 21st century. *J. Pediatr. Adolesc. Gynecol.* 25:289–94
9. Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, et al. 2000. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology* 11:641–47
10. Bonefeld-Jørgensen EC, Long M, Fredslund SO, Bossi R, Olsen J. 2014. Breast cancer risk after exposure to perfluorinated compounds in Danish women: a case-control study nested in the Danish National Birth Cohort. *Cancer Causes Control* 5:1439–48
11. Bonner MR, Han D, Nie J, Rogerson P, Vena JE, et al. 2005. Breast cancer risk and exposure in early life to polycyclic aromatic hydrocarbons using total suspended particulates as a proxy measure. *Cancer Epidemiol. Biomark. Prev.* 14:53–60
12. Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. 2007. Environmental pollutants and breast cancer: epidemiologic studies. *Cancer* 109:2667–711
13. Brody JG, Rudel RA, Michels KB, Moysich KB, Bernstein L, et al. 2007. Environmental pollutants, diet, physical activity, body size, and breast cancer: Where do we stand in research to identify opportunities for prevention? *Cancer* 109:2627–34
14. Brody JG, Tickner J, Rudel RA. 2005. Community-initiated breast cancer and environment studies and the precautionary principle. *Environ. Health Perspect.* 113:920–25
15. Brotons JA, Olea-Serrano MF, Villalobos M, Pedraza V, Olea N. 1995. Xenoestrogens released from lacquer coatings in food cans. *Environ. Health Perspect.* 103:608–12
16. Calafat AM, Kuklenyik Z, Reidy JA, Caudill SP, Ekong J, Needham LL. 2005. Urinary concentrations of bisphenol A and 4-nonylphenol in a human reference population. *Environ. Health Perspect.* 113:391–95
17. Calafat AM, Wong LY, Kuklenyik Z, Reidy JA, Needham LL. 2007. Polyfluoroalkyl chemicals in the U.S. population: data from the National Health and Nutrition Examination Survey (NHANES) 2003–2004 and comparisons with NHANES 1999–2000. *Environ. Health Perspect.* 115:1596–602
18. Calle EE, Frumkin H, Henley SJ, Savitz DA, Thun MJ. 2002. Organochlorines and breast cancer risk. *CA Cancer J. Clin.* 52:301–9
19. Cantor KP, Stewart PA, Brinton LA, Dosemeci M. 1995. Occupational exposures and female breast cancer mortality in the United States. *J. Occup. Envrion. Med.* 37:336–48
20. Carmichael A, Sami AS, Dixon JM. 2003. Breast cancer risk among the survivors of atomic bomb and patients exposed to therapeutic ionising radiation. *Eur. J. Surg. Oncol.* 29:475–79
21. Chlebowski RT. 2013. Vitamin D and breast cancer incidence and outcome. *Anticancer Agents Med. Chem.* 13:98–106

22. Chou YY, Huang PC, Lee CC, Wu MH, Lin SJ. 2009. Phthalate exposure in girls during early puberty. *J. Pediatr. Endocrinol. Metab.* 22:69–77
23. Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, et al. 2015. DDT exposure in utero and breast cancer. *J. Clin. Endocrinol. Metab.* 100:2865–72
24. Cohn BA, Terry MB, Plumb M, Cirillo PM. 2012. Exposure to polychlorinated biphenyl (PCB) congeners measured shortly after giving birth and subsequent risk of maternal breast cancer before age 50. *Breast Cancer Res. Treat.* 136:267–75
25. Cohn BA, Wolff MS, Cirillo PM, Sholtz RI. 2007. DDT and breast cancer in young women: new data on the significance of age at exposure. *Environ. Health Perspect.* 115:1406–14
26. Collab. Group Horm. Factors in Breast Cancer. 2002. Alcohol, tobacco and breast cancer—collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Br. J. Cancer* 87:1234–45
27. Conroy SM, Clarke CA, Yang J, Shariff-Marco S, Shvetsov YB, et al. 2017. Contextual impact of neighborhood obesogenic factors on postmenopausal breast cancer: the Multiethnic Cohort. *Cancer Epidemiol. Biomark. Prev.* 26:480–89
28. Conroy SM, Shariff-Marco S, Koo J, Yang J, Keegan TH, et al. 2017. Racial/ethnic differences in the impact of neighborhood social and built environment on breast cancer risk: the Neighborhoods and Breast Cancer Study. *Cancer Epidemiol. Biomark. Prev.* 26:541–52
29. Costantini AS, Gorini G, Consonni D, Miligi L, Giovannetti L, Quinn M. 2009. Exposure to benzene and risk of breast cancer among shoe factory workers in Italy. *Tumori* 95:8–12
30. Daniels K, Daugherty J, Jones J, Mosher W. 2015. Current contraceptive use and variation by selected characteristics among women aged 15–44: United States, 2011–2013. *Natl. Health Stat. Rep.* (86):1–14
31. de Kok IM, van Lenthe FJ, Avendano M, Louwman M, Coebergh JW, Mackenbach JP. 2008. Childhood social class and cancer incidence: results of the globe study. *Soc. Sci. Med.* 66:1131–39
32. Deardorff J, Ekwaru JP, Kushi LH, Ellis BJ, Greenspan LC, et al. 2011. Father absence, body mass index, and pubertal timing in girls: differential effects by family income and ethnicity. *J. Adolesc. Health* 48:441–47
33. Deierlein AL, Wolff MS, Pajak A, Pinney SM, Windham GC, et al. 2016. Longitudinal associations of phthalate exposures during childhood and body size measurements in young girls. *Epidemiology* 27:492–99
34. Denham M, Schell LM, Deane G, Gallo MV, Ravenscroft J, DeCaprio AP. 2005. Relationship of lead, mercury, mirex, dichlorodiphenyldichloroethylene, hexachlorobenzene, and polychlorinated biphenyls to timing of menarche among Akwesasne Mohawk girls. *Pediatrics* 115:e127–34
35. DeSantis C, Howlader N, Cronin KA, Jemal A. 2011. Breast cancer incidence rates in U.S. women are no longer declining. *Cancer Epidemiol. Biomark. Prev.* 20:733–39
36. Dodson RE, Perovich LJ, Covaci A, Van den Eede N, Ionas AC, et al. 2012. After the PBDE phase-out: a broad suite of flame retardants in repeat house dust samples from California. *Environ. Sci. Technol.* 46:13056–66
37. Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, et al. 2005. Pesticide use and breast cancer risk among farmers' wives in the Agricultural Health Study. *Am. J. Epidemiol.* 161:121–35
38. Falck F Jr., Ricci A Jr., Wolff MS, Godbold J, Deckers P. 1992. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch. Environ. Health* 47:143–46
39. Fenton SE. 2006. Endocrine-disrupting compounds and mammary gland development: early exposure and later life consequences. *Endocrinology* 147:S18–24
40. Ferlay J, Shin H, Bray F, et al. 2010. *GLOBOCAN 2008. Cancer incidence and mortality worldwide. IARC CancerBase No. 10* [Internet], *Version 2.0*. Int. Agency Res. Cancer, Lyon, Fr.
41. Gammon MD, John EM, Britton JA. 1998. Recreational and occupational physical activities and risk of breast cancer. *J. Natl. Cancer Inst.* 90:100–17
42. Gammon MD, Neugut AI, Santella RM, Teitelbaum SL, Britton JA, et al. 2002. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res. Treat.* 74:235–54
43. Gammon MD, Santella RM. 2008. PAH, genetic susceptibility and breast cancer risk: an update from the Long Island Breast Cancer Study Project. *Eur. J. Cancer* 44:636–40

44. Garcia E, Hurley S, Nelson DO, Hertz A, Reynolds P. 2015. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ. Health* 14:14
45. Gladen BC, Ragan NB, Rogan WJ. 2000. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene. *J. Pediatr.* 136:490–96
46. Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, et al. 2015. EDC-2: The Endocrine Society's second Scientific Statement on endocrine-disrupting chemicals. *Endocr. Rev.* 36:E1–150
47. Graham C, Cook MR, Gerkovich MM, Sastre A. 2001. Examination of the melatonin hypothesis in women exposed at night to EMF or bright light. *Environ. Health Perspect.* 109:501–7
48. Hart JE, Bertrand KA, DuPre N, James P, Vieira VM, et al. 2016. Long-term particulate matter exposures during adulthood and risk of breast cancer incidence in the Nurses' Health Study II Prospective Cohort. *Cancer Epidemiol. Biomarkers Prev.* 25:1274–76
49. Herbst AL, Ulfelder H, Poskanzer DC. 1971. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. *N. Engl. J. Med.* 284:878–81
50. Hiatt RA. 2008. Epidemiology: key to translational, team, and transdisciplinary science. *Ann. Epidemiol.* 18:859–61
51. Hiatt RA. 2011. Epidemiologic basis of the role of environmental endocrine disruptors and breast cancer. In *Environment and Breast Cancer*, ed. J Russo, pp. 1–27. New York: Springer Sci.+Bus. Media
52. Hiatt RA, Haslam SZ, Osuch J. 2009. The breast cancer and the environment research centers: transdisciplinary research on the role of the environment in breast cancer etiology. *Environ. Health Perspect.* 117:1814–22
53. Hiatt RA, Porco TC, Liu F, Balke K, Balmain A, et al. 2014. A multilevel model of postmenopausal breast cancer incidence. *Cancer Epidemiol. Biomark. Prev.* 23:2078–92
54. Holmes AK, Koller KR, Kieszak SM, Sjodin A, Calafat AM, et al. 2014. Case-control study of breast cancer and exposure to synthetic environmental chemicals among Alaska Native women. *Int. J. Circumpolar Health* 73:25760
55. Høyer AP, Grandjean P, Jørgensen T, Brock JW, Hartvig HB. 1998. Organochlorine exposure and risk of breast cancer. *Lancet* 352:1816–20
56. Hunter DJ, Colditz GA, Hankinson SE, Malspeis S, Spiegelman D, et al. 2010. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiol. Biomark. Prev.*19:2496–502
57. Hurley S, Reynolds P, Goldberg D, Nelson DO, Jeffrey SS, Petreas M. 2011. Adipose levels of polybrominated diphenyl ethers and risk of breast cancer. *Breast Cancer Res. Treat.* 129:505–11
58. IARC (Int. Agency Res. Cancer). 1987. *Overall Evaluations of Carcinogenicity. IARC Monographs on the Evalution of Carcinogenic Risks to Humans*. Lyon, Fr.: IARC, World Health Organ.
59. IARC (Int. Agency Res. Cancer). 2004. *Tobacco Smoke and Involuntary Smoking. IARC Monographs on the Evalution of Carcinogenic Risks to Humans*. Lyon, Fr.: IARC, World Health Organ.
60. IARC (Int. Agency Res. Cancer). 2008. *1,3-Butadiene, Ethylene Oxide and Vinyl Halides (Vinyl Fluoride, Vinyl Chloride and Vinyl Bromide). IARC Monographs on the Evalution of Carcinogenic Risks to Humans*. Lyon, Fr.: IARC, World Health Organ.
61. IARC (Int. Agency Res. Cancer). 2010. *Painting, Firefighting, and Shiftwork. IARC Monographs on the Evalution of Carcinogenic Risks to Humans*. Lyon, Fr.: IARC, World Health Organ.
62. IARC (Int. Agency Res. Cancer). 2016. *Outdoor Air Pollution. Monographs on the Evaluation of Carcinogenic Risks to Humans.* Lyon, Fr.: IARC, World Health Organ.
63. IBCERCC (Interagency Breast Cancer Environ. Res. Coord. Comm.). 2013. *Breast Cancer and the Environment: Prioritizing Prevention*. Research Triangle Park, NC: Natl. Inst. Environ. Health Sci. (NIEHS). **https://www.niehs.nih.gov/about/assets/docs/breast_cancer_and_the_environment_prioritizing_prevention_508.pdf**
64. IOM (Inst. Med.). 2012. *Breast Cancer and the Environment: A Life Course Approach*. Washington, DC: Natl. Acad. Press
65. Jemal A, Ward EM, Johnson CJ, Cronin KA, Ma J, et al. 2017. Annual report to the nation on the status of cancer, 1975–2014, featuring survival. *J. Natl. Cancer Inst.* 109:djx030
66. Johnson KC, Miller AB, Collishaw NE, Palmer JR, Hammond SK, et al. 2011. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk 2009. *Tob. Control* 20:e2

67. Kelsey JL, Gammon MD, John EM. 1993. Reproductive factors and breast cancer. *Epidemiol. Rev.* 15:36–47
68. Kogevinas M. 2001. Human health effects of dioxins: cancer, reproductive and endocrine system effects. *Hum. Reprod. Update* 7:331–39
69. Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, et al. 2015. Annual report to the nation on the status of cancer, 1975–2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J. Natl. Cancer Inst.* 107:djv048
70. Kolstad HA. 2008. Nightshift work and risk of breast cancer and other cancers—a critical review of the epidemiologic evidence. *Scand. J. Work Environ. Health* 34:5–22
71. Korde LA, Wu AH, Fears T, Nomura AM, West DW, et al. 2009. Childhood soy intake and breast cancer risk in Asian American women. *Cancer Epidemiol. Biomark. Prev.* 18:1050–59
72. Labrèche F, Goldberg MS, Valois MF, Nadon L. 2010. Postmenopausal breast cancer and occupational exposures. *Occup. Environ. Med.* 67:263–69
73. Laden F, Ishibe N, Hankinson SE, Wolff MS, Gertig DM, et al. 2002. Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the Nurses' Health Study. *Cancer Epidemiol. Biomark. Prev.* 11:1560–65
74. Lau C, Anitole K, Hodes C, Lai D, Pfahles-Hutchens A, Seed J. 2007. Perfluoroalkyl acids: a review of monitoring and toxicological findings. *Toxicol Sci.* 99:366–94
75. Lee SA, Shu XO, Li H, Yang G, Cai H, et al. 2009. Adolescent and adult soy food intake and breast cancer risk: results from the Shanghai Women's Health Study. *Am. J. Clin. Nutr.* 89:1920–26
76. Leung CW, Gregorich SE, Laraia BA, Kushi LH, Yen IH. 2010. Measuring the neighborhood environment: associations with young girls' energy intake and expenditure in a cross-sectional study. *Int. J. Behav. Nutr. Phys. Activity* 7:52
77. Liu R, Nelson DO, Hurley S, Hertz A, Reynolds P. 2015. Residential exposure to estrogen disrupting hazardous air pollutants and breast cancer risk: the California Teachers Study. *Epidemiology* 26:365–73
78. López-Carrillo L, Hernández-Ramírez RU, Calafat AM, Torres-Sánchez L, Galván-Portillo M, et al. 2010. Exposure to phthalates and breast cancer risk in northern Mexico. *Environ. Health Perspect.* 118:539–44
79. López-Cervantes M, Torres-Sánchez L, Tobías A, López-Carrillo L. 2004. Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. *Environ. Health Perspect.* 112:207–14
80. Ma H, Bernstein L, Pike MC, Ursin G. 2006. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. *Breast Cancer Res.* 8:R43
81. Mabry PL, Olster DH, Morgan GD, Abrams DB. 2008. Interdisciplinarity and systems science to improve population health: a view from the NIH Office of Behavioral and Social Sciences Research. *Am. J. Prev. Med.* 35:S211–24
82. Madigan MP, Ziegler RG, Benichou J, Byrne C, Hoover RN. 1995. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J. Natl. Cancer Inst.* 87:1681–85
83. Maffini MV, Rubin BS, Sonnenschein C, Soto AM. 2006. Endocrine disruptors and reproductive health: the case of bisphenol-A. *Mol. Cell Endocrinol.* 254–255:179–86
84. Maltoni C, Ciliberti A, Cotti G, Conti B, Belpoggi F. 1989. Benzene, an experimental multipotential carcinogen: results of the long-term bioassays performed at the Bologna Institute of Oncology. *Environ. Health Perspect.* 82:109–24
85. Manz A, Berger J, Dwyer JH, Flesch-Janys D, Nagel S, Waltsgott H. 1991. Cancer mortality among workers in chemical plant contaminated with dioxin. *Lancet* 338:959–64
86. Matthews JB, Twomey K, Zacharewski TR. 2001. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. *Chem. Res. Toxicol* 14:149–57
87. McElroy JA, Shafer MM, Trentham-Dietz A, Hampton JM, Newcomb PA. 2006. Cadmium exposure and breast cancer risk. *J. Natl. Cancer Inst.* 98:869–73
88. McGuinn LA, Voss RW, Laurent CA, Greenspan LC, Kushi LH, Windham GC. 2016. Residential proximity to traffic and female pubertal development. *Environ. Int.* 94:635–41

89. McKelvey W, Brody JG, Aschengrau A, Swartz CH. 2004. Association between residence on Cape Cod, Massachusetts, and breast cancer. *Ann. Epidemiol.* 14:89–94
90. Mettlin C. 1999. Global breast cancer mortality statistics. *CA: A Cancer J. Clin.* 49:138–44
91. Miller MD, Broadwin R, Green S, Marty MA, Polakoff J, et al. 2005. *Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Part B: Health Effects*. Sacramento: OEHHA (Calif. Environ. Health Hazard Assess.), Calif. Environ. Prot. Agency (CalEPA). **https://oehha.ca.gov/media/downloads/crnr/app3partb2005.pdf**
92. Morabia A. 2002. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. *Environ. Mol. Mutagen.* 39:89–95
93. Morello-Frosch R, Jesdale BM. 2006. Separate and unequal: residential segregation and estimated cancer risks associated with ambient air toxics in U.S. metropolitan areas. *Environ. Health Perspect.* 114:386–93
94. Morris JJ, Seifter E. 1992. The role of aromatic hydrocarbons in the genesis of breast cancer. *Med. Hypotheses* 38:177–84
95. Moysich KB, Shields PG, Freudenheim JL, Schisterman EF, Vena JE, et al. 1999. Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. *Cancer Epidemiol. Biomark. Prev.* 8:41–44
96. Naess O, Strand BH, Smith GD. 2007. Childhood and adulthood socioeconomic position across 20 causes of death: a prospective cohort study of 800,000 Norwegian men and women. *J. Epidemiol. Community Health* 61:1004–9
97. Natl. Acad. Sci., Eng., Med. 2017. *Using 21st Century Science to Improve Risk-Related Evaluations*. Washington, DC: Natl. Acad. Press
98. Natl. Res. Counc. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: Natl. Acad. Press
99. Nie J, Beyea J, Bonner MR, Han D, Vena JE, et al. 2007. Exposure to traffic emissions throughout life and risk of breast cancer: the Western New York Exposures and Breast Cancer (WEB) study. *Cancer Causes Control* 18:947–55
100. Niehoff NM, Nichols HB, White AJ, Parks CG, D'Aloisio AA, Sandler DP. 2016. Childhood and adolescent pesticide exposure and breast cancer risk. *Epidemiology* 27:326–33
101. Olea N, Pulgar R, Pérez P, Olea-Serrano F, Rivas A, et al. 1996. Estrogenicity of resin-based composites and sealants used in dentistry. *Environ. Health Perspect.* 104:298–305
102. Olsen GW, Butenhoff JL, Zobel LR. 2009. Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. *Reprod. Toxicol.* 27:212–30
103. Ouyang F, Perry MJ, Venners SA, Chen C, Wang B, et al. 2005. Serum DDT, age at menarche, and abnormal menstrual cycle length. *Occup. Environ. Med.* 62:878–84
104. Oyesanmi O, Snyder D, Sullivan N, Reston J, Treadwell J, Schoelles KM. 2010. *Alcohol Consumption and Cancer Risk: Understanding Possible Causal Mechanisms for Breast and Colorectal Cancers. Evidence Reports/Technology Assessments.* Rockville, MD: Agency for Healthc. Res. Qual.
105. Palmer JR, Wise LA, Hatch EE, Troisi R, Titus-Ernstoff L, et al. 2006. Prenatal diethylstilbestrol exposure and risk of breast cancer. *Cancer Epidemiol. Biomark. Prev.* 15:1509–14
106. Pan S, Yuan C, Tagmount A, Rudel RA, Ackerman JM, et al. 2016. Parabens and human epidermal growth factor receptor ligand cross-talk in breast cancer cells. *Environ. Health Perspect.* 124:563–69
107. Patisaul HB, Jefferson W. 2010. The pros and cons of phytoestrogens. *Front. Neuroendocrinol.* 31:400–19
108. Petralia SA, Vena JE, Freudenheim JL, Dosemeci M, Michalek A, et al. 1999. Risk of premenopausal breast cancer in association with occupational exposure to polycyclic aromatic hydrocarbons and benzene. *Scand. J. Work Environ. Health* 25:215–21
109. Petralia SA, Vena JE, Freudenheim JL, Michalek A, Goldberg MS, et al. 1999. Risk of premenopausal breast cancer and patterns of established breast cancer risk factors among teachers and nurses. *Am. J. Ind. Med.* 35:137–41
110. Pudrovska T, Anikputa B. 2012. The role of early-life socioeconomic status in breast cancer incidence and mortality: unraveling life course mechanisms. *J. Aging Health* 24:323–44
111. Purdue MP, Hutchings SJ, Rushton L, Silverman DT. 2015. The proportion of cancer attributable to occupational exposures. *Ann. Epidemiol.* 25:188–92

112. Reding KW, Young MT, Szpiro AA, Han CJ, DeRoo LA, et al. 2015. Breast cancer risk in relation to ambient air pollution exposure at residences in the Sister Study Cohort. *Cancer Epidemiol. Biomark. Prev.* 24:1907–9
113. Reynolds P, Goldberg D, Hurley S, Nelson DO, Largent J, et al. 2009. Passive smoking and risk of breast cancer in the California teachers study. *Cancer Epidemiol. Biomark. Prev.* 18:3389–98
114. Reynolds P, Hurley S, Goldberg DE, Anton-Culver H, Bernstein L, et al. 2004. Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J. Natl. Cancer Inst.* 96:29–37
115. Robert SA, Strombom I, Trentham-Dietz A, Hampton JM, McElroy JA, et al. 2004. Socioeconomic risk factors for breast cancer: distinguishing individual- and community-level effects. *Epidemiology* 15:442–50
116. Rodgers KM, Udesky JO, Rudel RA, Brody JG. 2017. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. *Environ. Res.* 160:152–82
117. Routledge EJ, White R, Parker MG, Sumpter JP. 2000. Differential effects of xenoestrogens on coactivator recruitment by estrogen receptor (ER) α and ERβ. *J. Biol. Chem.* 275:35986–93
118. Rudel RA, Attfield KR, Schifano JN, Brody JG. 2007. Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention. *Cancer* 109:2635–66
119. Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. 2011. Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. *Environ. Health Perspect.* 119:1053–61
120. Salehi F, Turner MC, Phillips KP, Wigle DT, Krewski D, Aronson KJ. 2008. Review of the etiology of breast cancer with special attention to organochlorines as potential endocrine disruptors. *J. Toxicol. Environ. Health B Crit. Rev.* 11:276–300
121. Santodonato J. 1997. Review of the estrogenic and antiestrogenic activity of polycyclic aromatic hydrocarbons: relationship to carcinogenicity. *Chemosphere* 34:835–48
122. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, et al. 2009. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. *Lancet Oncol.* 10:1033–34
123. Selevan SG, Rice DC, Hogan KA, Euling SY, Pfahles-Hutchens A, Bethel J. 2003. Blood lead concentration and delayed puberty in girls. *N. Engl. J. Med.* 348:1527–36
124. Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB. 2017. Dependence of cancer risk from environmental exposures on underlying genetic susceptibility: an illustration with polycyclic aromatic hydrocarbons and breast cancer. *Br. J. Cancer* 116:1229–33
125. Shu XO, Jin F, Dai Q, Shi JR, Potter JD, et al. 2001. Association of body size and fat distribution with risk of breast cancer among Chinese women. *Int. J. Cancer* 94:449–55
126. Shui I, Giovannucci E. 2014. Vitamin D status and cancer incidence and mortality. *Adv. Exp. Med. Biol.* 810:33–51
127. Smith-Bindman R, Lipson J, Marcus R, Kim KP, Mahesh M, et al. 2009. Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. *Arch. Intern. Med.* 169:2078–86
128. Solomon GM, Morello-Frosch R, Zeise L, Faust JB. 2016. Cumulative environmental impacts: science and policy to protect communities. *Annu. Rev. Public Health* 37:83–96
129. Steenland K, Fletcher T, Savitz DA. 2010. Epidemiologic evidence on the health effects of perfluorooctanoic acid (PFOA). *Environ. Health Perspect.* 118:1100–8
130. Steenland K, Whelan E, Deddens J, Stayner L, Ward E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). *Cancer Causes Control* 14:531–39
131. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, et al. 2009. A review of human carcinogens—Part C: metals, arsenic, dusts, and fibres. *Lancet Oncol.* 10:453–54
132. Strand BH, Kunst A. 2007. Childhood socioeconomic position and cause-specific mortality in early adulthood. *Am. J. Epidemiol.* 165:85–93
133. Sturgeon SR, Schairer C, Grauman D, El Ghormli L, Devesa S. 2004. Trends in breast cancer mortality rates by region of the United States, 1950–1999. *Cancer Causes Control* 15:987–95

134. Suzuki R, Orsini N, Mignone L, Saji S, Wolk A. 2008. Alcohol intake and risk of breast cancer defined by estrogen and progesterone receptor status—a meta-analysis of epidemiological studies. *Int. J. Cancer* 122:1832–41
135. Teitelbaum SL, Belpoggi F, Reinlib L. 2015. Advancing research on endocrine disrupting chemicals in breast cancer: expert panel recommendations. *Reprod. Toxicol.* 54:141–47
136. Terry PD, Goodman M. 2006. Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. *Cancer Epidemiol. Biomark. Prev.* 15:602–11
137. Titus-Ernstoff L, Egan KM, Newcomb PA, Ding J, Trentham-Dietz A, Greenberg ER. 2002. Early life factors in relation to breast cancer risk in postmenopausal women. *Cancer Epidemiol. Biomark. Prev.* 110:207–10
138. Troisi R, Hatch EE, Titus-Ernstoff L, Hyer M, Palmer JR, et al. 2007. Cancer risk in women prenatally exposed to diethylstilbestrol. *Int. J. Cancer* 121:356–60
139. US DHHS (Dep. Health Hum. Serv.), CDC (Cent. Dis. Control Prev.), Off. Smok. Health. 2010. *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. Atlanta: CDC
140. van den Bosch M, Ode Sang A. 2017. Urban natural environments as nature-based solutions for improved public health—a systematic review of reviews. *Environ. Res.* 158:373–84
141. Vasiliu O, Muttineni J, Karmaus W. 2004. In utero exposure to organochlorines and age at menarche. *Hum. Reprod.* 19:1506–12
142. Warner M, Mocarelli P, Samuels S, Needham L, Brambilla P, Eskenazi B. 2011. Dioxin exposure and cancer risk in the Seveso Women's Health Study. *Environ. Health Perspect.* 119:1700–5
143. White AJ, Teitelbaum SL, Wolff MS, Stellman SD, Neugut AI, Gammon MD. 2013. Exposure to fogger trucks and breast cancer incidence in the Long Island Breast Cancer Study Project: a case-control study. *Environ. Health* 12:24
144. Willett WC. 2001. Diet and breast cancer. *J. Intern. Med.* 249:395–411
145. Windham GC, Bottomley C, Birner C, Fenster L. 2004. Age at menarche in relation to maternal use of tobacco, alcohol, coffee, and tea during pregnancy. *Am. J. Epidemiol.* 159:862–71
146. Windham GC, Pinney SM, Sjodin A, Lum R, Jones RS, et al. 2010. Body burdens of brominated flame retardants and other persistent organo-halogenated compounds and their descriptors in US girls. *Environ. Res.* 110:251–57
147. Wolff MS. 2006. Endocrine disruptors: challenges for environmental research in the 21st century. *Ann. N. Y. Acad. Sci.* 1076:228–38
148. Wolff MS, Britton JA, Boguski L, Hochman S, Maloney N, et al. 2008. Environmental exposures and puberty in inner-city girls. *Environ. Res.* 107:393–400
149. Wolff MS, Camann D, Gammon M, Stellman SD. 1997. Proposed PCB congener groupings for epidemiological studies. *Environ. Health Perspect.* 105:13–14
150. Wolff MS, Collman GW, Barrett JC, Huff J. 1996. Breast cancer and environmental risk factors: epidemiological and experimental findings. *Annu. Rev. Pharmacol. Toxicol.* 36:573–96
151. Wolff MS, Teitelbaum SL, Pinney SM, Windham G, Liao L, et al. 2010. Investigation of relationships between urinary biomarkers of phytoestrogens, phthalates, and phenols and pubertal stages in girls. *Environ. Health Perspect.* 118:1039–46
152. Wolff MS, Teitelbaum SL, Windham G, Pinney SM, Britton JA, et al. 2007. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. *Environ. Health Perspect.* 115:116–21
153. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. 1993. Blood levels of organochlorine residues and risk of breast cancer. *J. Natl. Cancer Inst.* 85:648–52
154. World Cancer Res. Fund, Am. Inst. Cancer Res. 2007. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: Am. Inst. Cancer Res. **http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf**
155. World Cancer Res. Fund, Am. Inst. Cancer Res. 2010. *Breast Cancer 2010 Report: Food, Nutrition, Physical Activity, and the Prevention of Breast Cancer*. Washington, DC: Am. Inst. Cancer Res. **http://www.wcrf.org/sites/default/files/Breast-Cancer-2010-Report.pdf**

156. Wu AH, Yu MC, Tseng CC, Pike MC. 2008. Epidemiology of soy exposures and breast cancer risk. *Br. J. Cancer* 98:9–14
157. Wu T, Buck GM, Mendola P. 2003. Blood lead levels and sexual maturation in U.S. girls: the Third National Health and Nutrition Examination Survey, 1988–1994. *Environ. Health Perspect.* 111:737–41
158. Wu T, Mendola P, Buck GM. 2002. Ethnic differences in the presence of secondary sex characteristics and menarche among US girls: the Third National Health and Nutrition Examination Survey, 1988–1994. *Pediatrics* 110:752–57
159. Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. 2010. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. *Environ. Health Perspect.* 118:60–66
160. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, et al. 2011. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. *J. Natl. Cancer Inst.* 103:250–63
161. Ye X, Bishop AM, Reidy JA, Needham LL, Calafat AM. 2006. Parabens as urinary biomarkers of exposure in humans. *Environ. Health Perspect.* 114:1843–46
162. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, et al. 1993. Migration patterns and breast cancer risk in Asian-American women. *J. Natl. Cancer Inst.* 85:1819–27
163. Zota AR, Rudel RA, Morello-Frosch RA, Brody JG. 2008. Elevated house dust and serum concentrations of PBDEs in California: unintended consequences of furniture flammability standards? *Environ. Sci. Technol.* 42:8158–64