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Review

The effect of environment on breast cancer risk

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Summary

Environmental factors are believed to explain a large proportion of breast cancer incidence. Known risk factors for breast cancer, which are related to the reproductive life of women, and other factors, such as inheritance and socioeconomic status, explain only about half of the breast cancer cases in the US. Ionizing radiation is a well established environmental risk factor for breast cancer. Chemicals that induce mammary cancer in rodents have served as leads for studies in humans, but occupational and environmental exposure to these chemicals have for the most part lacked association with breast cancer risk. However, there is recent evidence in rats that cadmium at very low doses acts as an estrogen mimic, indicating a need to investigate the effects of metals on breast cancer risk. Studies suggest that circadian rhythm disruption is linked with breast cancer, but too few studies have been done to be conclusive. Over the years, cigarette smoking as a risk factor for breast cancer has remained controversial. However, recent research has found passive smoke exposure to be associated with increased breast cancer risk, which is hypothesized to be accounted for on the basis of an antiestrogenic effect of smoking. Solar radiation has been noted to be associated with reduced breast cancer, supporting the hypothesis that vitamin D plays a protective role in reducing this risk. Although, most of the environmental factors discussed in this review have not been convincingly found to influence breast cancer risk, research suggests that environmental exposure in combination with genetic pre-disposition, age at exposure, and hormonal milieu have a cumulative effect on breast cancer risk.

Introduction

Breast cancer is the most common malignancy in women, both in the developed and developing world, with annual incidence rates ranging from 11.8 per 100,000 in eastern China to 86.3 per 100,000 in North America [1]. In US women, breast cancer incidence rates have been rising slowly for the past two decades [1–3], which is not likely to be entirely explained by increased mammogram screening. Furthermore, studies indicate that as populations migrate from the low to high-risk geographical areas the incidence of breast cancer approaches that of the host country in one or two generations [1–3].

Female gender, age, and country of birth are the strongest determinants of breast cancer risk. The known risk factors for breast cancer are primarily related to the reproductive cycle (early age at menarche, nulliparity, late age at first full-term pregnancy, late age at lactation and short duration, and late menopause) and inheritance (e.g., *BRCA*1 and *BRCA*2 gene mutations). Other known risk factors are exogenous estrogens, radiation, alcohol consumption, and higher educational level and socioeconomic status [3]. Most of these risk factors are linked with a cumulative exposure to estrogen.

Known risk factors for breast cancer (excluding exogenous estrogen use, radiation exposure, and alcohol consumption), are estimated to explain only 25–47% of breast cancer in the US [4, 5]. It is estimated that another 1% of breast cancers in the US may be attributable to diagnostic radiography [6]. In addition, studies of twins and of families with cancer in Sweden, Denmark, and Finland have indicated that greater than 60% of breast cancer has an environmental etiology [7, 8]. Because of the results of these studies and the inability to explain the causes for the increasing incidence of breast cancer and its geo-

graphical variation, greater attention has been focused on the role that the environment plays in the etiology of breast cancer. In fact, most scientists now believe that breast cancer is the result of a complex interaction of internally and externally introduced factors, all played upon by the element of time [9]. This review will present a summary of the scientific evidence in relation to the effect of environment on breast cancer risk.

The biological basis for the investigation of breast cancer and the environment is broad. Based on previous clinical observation, the guiding hypothesis for this research has been that estrogen plays a major role in the genesis of breast cancer [10–12]. However, human studies have been inconsistent in establishing a link between high estrogen levels and breast cancer risk [13], and past *in vitro* models have not identified the specific role of estrogen in the initiation and progression of breast cancer [14]. The classic two-step animal model of chemical carcinogenesis, which may or may apply to breast cancer development, asserts that chemical carcinogens convert normal cells into genetically altered cells or pre-cancerous cells (initiation), and that the pre-cancerous cells can be converted to cancerous cells (progression) after exposure to epigenetic influences, such as estrogen [14]. Therefore, it is thought that non-estrogenic environmental carcinogens, either physical or chemical (e.g., excess ionizing radiation, man-made chemicals, or biological agents such as viruses), which may cause genetic alterations, may also play an important role in the development of breast cancer [14].

Environmental chemical exposures relevant for breast cancer etiology

A number of environmental chemicals that cause mammary cancer in rodents – such as solvents and pesticides – that enhance tumor growth, or are genotoxic have been investigated with respect to their potential influence on breast cancer risk [15, 16]. These chemicals may be broadly classified as tumor initiators (mutagens or genotoxic) or tumor promoters ('endocrine disruptors' or environmental estrogens) that act at many junctures during the genesis of breast cancer. An endocrine disruptor is a chemical that interferes with the functioning of the endocrine system by mimicking a hormone, blocking the effects of the hormone, or by stimulating or inhibiting the production or transport of hormones [17]. Many of these chemicals are more likely to be encountered in an industrial environment than in other settings, such as the household environment that women experience daily. However, in a recent survey, 86 potential mammary toxins were identified and measured in household dust and air, including nine mammary carcinogens and 77 hormonally active agents or closely related compounds. Of these, more than 30% were detected in the three homes surveyed during the pilot study for this survey [18].

Although, a large variety of compounds currently in general use are analogs to known mammary carcinogens for rodents, few have been tested for their carcinogenic potential. Other chemicals, such as dichlorodiphenyltrichloroethane (DDT), polychorinated biphenyls (PCBs), and atrazine that are not causally associated with breast cancer in humans are known to enhance or inhibit tumor growth in rodents [19, 20]. The organochlorines (OCs), including DDT, PCBs, dioxin, polybrominated biphenyls (PBBs), and phenoxy acids as well as solvents, may also reduce cell-mediated immune function, which may increase susceptibility to developing breast cancer [21]. As a result, a number of environmental chemicals have been investigated in epidemiological studies with respect to their potential influence on breast cancer risk.

Occupational studies

Occupational exposure to environmental chemicals usually are typically higher than those in other surroundings, providing the opportunity to determine cancer risk among workers, either by identifying work-related exposures within specific cancer types or by assessing cancer occurrence within jobs that have known chemical or physical contamination. Several occupations have been linked with breast cancer risk by at least one epidemiological study [22]. Evidence that chemical exposures may increase the risk for breast cancer incidence or mortality has been most striking for the white collar or professional and managerial occupations; clerical, secretarial and related jobs; teachers; nurses; scientists; physicians and other healthcare professionals; and clergy [22]. However, it is not obvious that these jobs would have high carcinogenic exposures.

There have been many limitations to the occupational studies, as reviewed by Goldberg and Labreche [22]. Of primary concern for many of these studies are the following: (1) imprecise or poorly classified exposures or disease status, which is likely to result in attenuated risk estimates, (2) the examination of

breast cancer mortality rather than incidence making the results misleading with regard to understanding etiology because the women who survive the disease are excluded, (3) the lack of statistical adjustment for confounders, such as the reproductive risk factors for breast cancer (menopausal status, age at menarche, parity, age at first full-term birth, and lactation history), which can overestimate or underestimate study findings, and (4) the occupational cohorts often had too few women diagnosed with breast cancer, whereas case-control studies often have too few women within a given occupational group available for analyses, thus reducing statistical power to examine the hypotheses.

Organochlorines

Several recent investigations have assessed exposure to persistent OCs in relation to breast cancer risk. OCs are a diverse group of synthetic chemicals, many of which were released into the environment in past decades through their use as pesticides or industrial products. The most abundant of these environmental contaminants are the pesticide DDT and the PCBs, which were introduced in the US in 1945 and banned in the US in 1972 [23]. DDT was used widely in the US for insect control in forestry, agriculture, and building protection from 1945 until the early 1960s [23]. PCBs were extensively used in the US as dielectric fluids in transformers and capacitors, plasticizers, lubricants, and heat transfer fluids, and in the manufacture of products, such as paints and paper until their use was discontinued in the US in 1977. Dioxins are also OCs that are reproduced as combustion byproducts for industrial processes or as contaminants of herbicides. The biological basis for linking their exposure to breast cancer involves their considerable use, and use patterns, their persistence, their potential to act as endocrine disruptors (i.e., weakly estrogenic or antiestrogenic in experimental assays), and their carcinogenicity in animals [24–26].

OCs degrade slowly, are lipid soluble, bioaccumulate in the food chain, and may be found in human adipose tissue, blood, and breast milk. The most prevalent OC residues found in human tissues are dichlorodiphenyldichloroethane (DDE), the major metabolite of DDT, and PCBs. Since OCs are particularly persistent, with biological half-lives of many years, it is believed that current blood and adipose tissue levels can be used to reflect cumulative exposures. Although DDE is a weak antiestrogen, the rationale for using it as a biological marker is that it is a major degradation product of DDT and has been shown to reflect long-term exposure to DDT [27].

In 1993, a case-control study conducted by Wolff and colleagues in New York found two to four-fold elevations in the occurrence of breast cancer among women with the highest serum levels of DDE and PCBs compared to those with the lowest levels [28]. Before 1993, the possible association between adipose tissue (breast and elsewhere) or blood OC levels and breast cancer had been examined in only a few small studies, most of which examined OC levels in the breast tissue. The results from these studies were inconsistent, but overall did not show a positive correlation with OCs and breast cancer risk. Since the results of this study was published, nearly 30 published studies have attempted to replicate its results. With rare exceptions, there is consistent evidence from many methodologically sound studies showing no association between levels of persistent OC compounds, notably DDE and PCBs (total and individual congeners), and breast cancer [29–33]. The lack of association has been observed in an ecological study, in case-control studies, in prospective follow-up studies, in studies of serum, plasma and adipose tissue (breast or elsewhere), and in studies conducted in the US, Canada, Europe, and elsewhere [34–61]. However, a few studies have shown higher breast cancer risk or a protective effect from breast cancer from individual PCB congeners. The PCB congeners that had a protective effect for breast cancer were presumed to have antiestrogenic effects [58, 59].

Many studies have been conducted in the US to address the possibility that exposure to OCs may explain the higher rates of breast cancer observed there [38, 39, 41, 43, 47, 50, 58]. Collectively, results from these studies indicate that women with breast cancer have the same blood levels of DDE and PCBs as women without breast cancer. A pooled analysis of 1400 cases from five of these studies did not find an increased risk of breast cancer with exposure to OCs when adjusted for race [60].

Only one study to date has the potential to look at age-dependent OC exposure and breast cancer risk [33]. This study examined the association between individual serum levels of dioxin and breast cancer risk in women residing around Sveso, Italy, in 1976, at the time of an industrial explosion that resulted in the highest known population exposure to dioxin. This cohort was comprised of 981 women who were infants to 40 years old in 1976 and resided in the most contaminated areas at the time of the explosion. Dioxin

levels were measured using archived serum collected soon after the explosion. At the time of the explosion, 24% women were younger than 10 years old and 29% were pre-menarchal. Although the number of breast cancer cases in this study was small ($n = 15$), a recent follow-up of the study (20 year follow-up) indicated that dioxin levels were associated with an increase in breast cancer incidence among women in this cohort. Future follow-ups of this study will be instructive for assessing the importance of age at OC exposure as a risk factor for breast cancer.

While exposure to OC compounds does not appear to increase the risk of breast cancer overall, several investigators have examined their influence on the risk for breast cancer in subgroups of women in regards to race, menopausal status, history of parity and breastfeeding, hormone replacement therapy use, body mass, tumor characteristics (e.g., estrogen and progesterone receptor positivity and negativity), and variants of metabolizing genes (e.g., Cytochrome P450) [35, 39, 43–45, 47, 49, 50, 59, 62–64]. No consistent subgroup findings have emerged.

Although there is consistency of findings across the above epidemiological studies and these studies also relied on measured levels of the OCs rather then reported exposures, there are potential limitations to these studies. First, an important question is whether contemporary measurements of OC body burdens can adequately reflect past exposures. If not, the differences between cases and controls might be missed, obscuring a true association between exposure and disease. Present evidence suggests that DDE has a half-life of 7–11 years and PCBs a half-life of 5–25 years [51]. The time lapse between exposure and sample collection is an issue since the PCB congeners with the highest potential estrogenicity are more quickly metabolized [65]. In addition, the inconsistency in the results of the studies that assessed breast cancer risk related to PCB exposure may be due to counteracting estrogenic and antiestrogenic effects. Another potentially important limitation of these studies is that no association between OC exposure and breast cancer was demonstrated because the critical age of exposure was not assessed. It has been suggested that the time period to the first pregnancy, as well as childhood or adolescence may be the critical period of exposure to carcinogenic agents due to the vulnerability of the undifferentiated breast cells, as noted in women that survived the atomic bombings or had undergone other medical therapy involving large does of ionizing radiation [66–68]. Future follow-ups of the Sveso, Italy cohort above [32] will be instructive for assessing the importance of age at OC exposure as a risk factor for breast cancer. Finally, another potential confounding factor was that many of the larger well-controlled case-control studies used women with benign breast disease (BBD) as controls. There is some evidence that women with a previous history of BBD have a higher risk for breast cancer [69]. Except for one study, none of the studies that used women with BBD as controls found a positive relationship between levels of OCs and breast cancer risk [29].

Organic solvents and other chemicals

Certain organic solvents have been reported to be carcinogens in animals and some are mammary carcinogens [15]. These chemicals are ubiquitous both in the environment and in the workplace. They are used in the manufacture of glues, paints, varnishes, various chemicals, and constitute the major chemicals used in dry cleaning and metal degreasing. Several occupations involve exposure to solvents, such as printing and publishing, the solvent-using industries, mechanics, and laundry and dry cleaning workers. In a case control study by Band and colleagues that adjusted for all of the known risk factors for breast cancer, several significant associations between breast cancer incidence and occupations that entail exposures to solvents and pesticides (laundry and dry cleaners, aircraft workers, automotive repair workers, and gasoline service station workers, crop farming, and publishing and printing) were noted [70]. Several other analytic epidemiological studies have been published on the solvent related jobs related to the incidence of breast cancer.

The laundry and dry cleaning industry has used several organic solvents over the years, with tetrachloroethylene being the most prevalently used nowadays [71]. As mentioned previously, only one case-control study that adjusted for all of the known breast cancer risk factors assessed breast cancer risk with this occupational exposure, found an increased risk for post-menopausal breast cancer in those working in the laundry and dry cleaning business [70].

A cohort study of women employed in coiling and wire drawing in the manufacturing of light bulbs (adjusted for age and calendar menstrual period) had an excess of breast cancer incidence among those who worked more than 5 years in the coiling and wire drawing department; methylene chloride and trichloroethylene were the solvents used [72]. In another

cohort study in which female shoe manufacturers were exposed to benzene and other chlorinated solvents (adjusted for age and race), it was found that incidence rates for breast cancer were not significantly elevated when the first exposure was assessed $\geq$20 years later [73]. In another cohort study, adjusted for age only, no increased risk for breast cancer was found among workers who were regularly monitored for exposure to organic solvents in Finland [74]. However, in a Swedish cohort study of oil refinery workers adjusted only for age, an increased risk for breast cancer incidence was noted [75]. In the study by Band and colleagues, increased breast cancer incidence was noted among post-menopausal women in the aircraft, automotive, and gasoline service station industries [70].

A population-based case-control study in the state of Washington, adjusted for age, parity, education, and alcohol intake reported a non-significant increase in breast cancer incidence among females in the occupational group of painters, sculptors and printmakers [76]. In the case-control study by Band and colleagues, increased breast cancer risk was noted in pre- and post-menopausal women working in the publishing and printing industry [70]. In a population-based case-control study that involved four states in the US (Maine, Massachusetts, New Hampshire, and Wisconsin), adjusted for state, age, reproductive risk factors, family history of breast cancer, BBD, education, body mass index (BMI) and alcohol consumption, there was no significant increase in breast cancer risk among women working in the precision production jobs [77].

A few ecological studies have assessed the risk of breast cancer with environmental exposures from organic chemicals, but theses associations may be the result of confounding factors [78]. In North Carolina, halomethanes in drinking water (chlorination byproducts of water treatment) were quantified by zip code but were not found to be associated significantly with breast cancer [79]. A study of women on Long Island, New York, in which the residence location of women in a case-control study of breast cancer linked with proximate high traffic sites or chemical facilities with carcinogen emissions, found a significantly higher risk among post-menopausal women living closer to the sources of exposure [80]. In Massachusetts, case-control studies that investigated the contamination of municipal water supplies with tetrachlorethylene related to breast cancer incidence there were suggestions of positive associations with breast cancer risk [81].

Although, these studies suffer many of the same shortcomings as the occupational studies above, such as adjusting for reproductive history and having to rely on historical assessment of solvent exposure (organic solvents are short-lived in the body), these studies collectively suggest positive associations between organic solvent exposures and breast cancer risk.

Metals

An epidemiological study that included the mortality records from 24 states, gathered from 1984 to 1989 coded for occupation and industry (excluding homemakers) suggested that metals and metal-related exposures were associated with breast cancer risk (odd ratios [ORs], 1.05–1.16) [82]. In a series of recent studies by Martin and colleagues, it was shown that several metal ions demonstrated estrogenic activity [83]. In experiments on MCF-7 breast cancer cells, these investigators showed that divalent cadmium, copper, cobalt, nickel, lead, mercury, tin and chromium ions, as well as arsenic, selenite and vanadate activated responses mediated by estrogen receptor-α (ERα). In addition, it was found that the metalloestrogen-induced activation of ERα was more potent than it was for the phytoestrogens, most environmental estrogenic chemicals of concern, and the selective estrogen receptor modulators used for the treatment of hormone dependent cancers and estrogen deficiencies in women. To demonstrate whether metals may have estrogen effects in the whole animal, Martin and colleagues [84] conducted a study in which female rats were exposed to an environmentally relevant dose of cadmium and measured the estrogen-like activity in the target organs. This study showed that cadmium induced several well-characterized estrogenic responses, such as increased uterine weights, hyperplasia and hypertrophy of the endometrial lining, and increased mammary epithelial density. These results indicate a need to further investigate the effects of metals on breast cancer risk.

Other environmental exposures relevant for breast cancer etiology

Ionizing radiation

Ionizing radiation is the most well established environmental risk factor for breast cancer. Increased rates of breast cancer have been found in laboratory animals and in human populations that have received

relatively high doses of ionizing radiation [66–68]. Much of the human evidence comes from the epidemiological studies of survivors of the atomic bomb blasts in Hiroshima and Nagasaki who were exposed to gamma radiation and from follow-up studies of cohorts of women who received various forms of treatment by X-radiation for diagnostic and therapeutic procedures. Women who survived the atomic bombings or who had undergone fluoroscopically guided treatments for tuberculosis have a 1.4 to 2.2-fold increased risk for developing cancer [85]. Women irradiated as treatment for post-partum mastitis were found to have a two-fold risk for developing breast cancer as compared to non-irradiated mastitis patients and non-irradiated sister controls [86, 87]. Age that the radiation exposure takes place may be the strongest determinant of risk, since nearly all the excess risk occurs among women who were exposed during adolescence and were diagnosed with breast cancer at a relatively young age [88, 89]. Furthermore, in a study of childhood survivors of cancer, 68% of whom received radiation therapy, breast cancer was found to be the most common of all the second malignancies regardless of gender [90].

Cosmic radiation

Pilots and fight attendants have been studied for cancer risk related to their exposure to cosmic radiation. Neutrons contribute a large proportion (up to 60%) of the effective dose from cosmic irradiation and are considered to have a greater biological effect than gamma radiation. However, there are few available data on the carcinogenic effect of neutrons in humans [86]. There were increases in breast cancer incidence and mortality among flight attendants in one cohort study ($n = 1690$ with 1532 women) [92] and in a record linkage study ($n = 1764$ with 1577 women) [93], but not in another cohort study ($n = 20{,}551$ with 16,014 women) [94]. Collectively, these studies suggest that there is an increased risk for breast cancer among flight attendants that is occupation related. However, the role played by the occupational exposure, that is, cosmic radiation, disturbance of circadian rhythm, electromagnetic force (EMF), and jet fuel exposure, or a combination of these factors is still a puzzle, as the confounding due to parity was ruled out in one of these studies [95].

Electromagnetic fields

Another environmental exposure that has been examined in relation to breast cancer is EMFs, a source of non-ionizing radiation. Mechanistically, it has been theorized that exposures to EMFs may cause increased risk of breast cancer through suppression of melatonin production [96]. The pineal gland regulates levels of melatonin, a hormone that plays a complex role in the regulation of the reproductive cycle. In rodents, studies of disruption of melatonin production caused by exposure to light produce a higher incidence of mammary tumors in the exposed rodents compared to their controls. Changes in serum prolactin and estrogenic levels were noted in the light-exposed animals [97].

In several studies of male breast cancer, an elevated risk was observed among men employed in either electrical [98, 99] telephone [100], or railroad [101] occupations that have been linked with higher EMF exposure. Although some studies of female workers in occupations with higher EMF exposure support the association of EMF and breast cancer risk [102, 103], most do not, as reviewed by Caplan and colleagues [104]. Furthermore, the inconsistent findings for studies examining other sources of EMF exposure, such as residential proximity to power lines [105–108] or electric blanket use [109–113], do not appear to corroborate a harmful relationship between EMF exposure and breast cancer risk. A major methodological issue for these studies was the inability to accurately measure EMF exposure.

Solar radiation

Generally, throughout the world, populations at high risk for breast cancer are also at high risk for colon cancer, and those at low risk for breast cancer are typically at low risk for colon cancer [114–117]. An inverse relationship of colon cancer with exposure to mean daily solar radiation (an indirect measure of ultraviolet-B light which can create the active form of vitamin D in the skin), or the intake of vitamin D and calcium has been observed [118, 119]. Based on the hypothesis that vitamin D plays a protective role in reducing the risk of breast cancer, an ecological study was performed that involved 20 Canadian cites, in which the association between acid haze air pollution, which blocks ultraviolet-B light, was examined. This study found that there was a statistically significant and positive association between this type of air pollution and age-adjusted mortality rates for colon cancer in women and men, and breast cancer in women [120]. These findings were duplicated in an ecological study conducted in the US [121] and the former Soviet Union [122]. A recent ecological study, conducted by

Grant using breast cancer mortality rates from 1989 to 1996, for 35 countries (include developed Western countries) found a negative association of breast cancer mortality rates with solar ultraviolet-B light [123]. In a cohort of white women derived from the first National Health and Nutrition Examination Survey (N-HANES) Epidemiologic Follow-up Study, that included 179 breast cancer incident cases, it was shown that the risk reductions for breast cancer were highest for those that lived in US regions of high solar radiation [124].

Circadian rhythm disruption

Suppression of the normal nocturnal production of melatonin by the pineal gland, could increase the release of estrogen by the ovaries, which may in turn increase the risk for breast cancer [96]. In a case-control study by Davis, Mirick, and Stevens it was concluded that breast cancer risk was increased among subjects who frequently did not sleep during the period of the night when the melatonin levels are typically at their highest [125]. In another study, that included 10 years of follow-up in the Nurse's Health Study cohort, it was concluded that working on rotating night shifts was associated with a moderately increased breast cancer risk among the female nurses in the cohort [126]. These studies indicate that it is necessary to further explore the relationship between light exposure and cancer risk through the melatonin pathway.

Tobacco smoke

Tobacco smoke is the major causative agent in the development of lung cancer [127]. Furthermore, cigarette smoke is a potent mammary gland carcinogen for rodents (polycyclic aromatic hydrocarbons [PAHs] , heterocyclic aromatic amines [HAAs], and *N*-nitrosamines) [128, 129], and is a human carcinogen for other organs (e.g., lung, bladder, and lymphatic system) [130]. Most importantly, cigarette smoke exposure is preventable.

In contrast, the possible role of smoking as a risk factor for breast cancer has remained controversial. Although, a higher prevalence of DNA adducts and *P*53 gene mutations have been reported to occur in the breast tissue of smokers compared with non-smokers [131–137], epidemiological studies, in general, have not shown cigarette smoking to be associated with increased breast cancer risk. In fact, most of the epidemiological studies that were conducted during the 1980's and early 1990's showed null or inverse associations of smoking with breast cancer risk [138, 139]. It is thought that the reduced breast cancer risk noted with some of these studies might be accounted for on the basis of an antiestrogenic effect of smoking, lowering the age of menopause and total estrogen exposure [140–142]. However, recent studies suggest that there may be increased breast cancer risk with smoking during pregnancy [143] and with passive smoking [138].

During the past 10 years, the effect of environmental tobacco smoke on human health has become an important public health issue. Several recent epidemiological studies have examined the breast cancer risk of passive smokers with never-active and never-passive smokers. Six out of 11 of these studies found ORs of 1.5 or greater with 95% confidence intervals ranging between 1.0 and 4.6 [138]. In a recent population-based case-control study by Kropp and Chang-Claude, that involved 468 pre-menopausal breast cancer patients and 1093 controls, it was noted that exposure to passive smoke in those that were not cigarette smokers was associated with the highest breast cancer risk, as compared to former, current, and ever active cigarette smokers, with ORs of 1.6 (95% CI: 1.1, 2.4), 1.2 (OR, 95% CI 0.8, 1.7), 1.5 (95% CI: 1.0, 2.2), and 1.3 (95% CI: 0.9, 1.9), respectively [144]. In addition, breast cancer risk associated with passive and active cigarette smoking was additive, with an OR of 1.8 (95% CI: 1.2, 2.7). This study also noted that exposure to tobacco smoke during childhood or before the first pregnancy did not appear to increase breast cancer risk. Likewise, in another case control study that was nested within the Nurse's Health Study cohort, a positive association with cigarette smoking before the first-term pregnancy and breast cancer risk was not found [145].

Furthermore, the carcinogenic effects of compounds found in passive smoke have been hypothesized to be stronger or weaker according to genotypes that either biologically activate or detoxify these compounds in the human body [146]. Two studies showed that passive smoking was associated with a higher breast cancer risk in those that were rapid versus slow acetylators related to the *N*-acetyltransferase 2 (*NAT2*) gene [147, 148]. Thus, it appears that breast cancer risk may be higher related to passive smoke as opposed to active smoke, and that this risk may be higher in individuals with specific metabolizing gene variants [149].

The above studies on passive smoking and breast cancer risk and the suggestions that this risk may be increased risk among women with certain genotypes requires confirmation in future epidemiological studies. In addition, more research is needed to determine the effect of cigarette smoking on breast cancer risk at different stages in a woman's lifecycle, such as during pregnancy.

Viral infection

Investigating viruses as possible etiologic factors for several disease has recently regained popularity. One hypothesis suggests that late exposure to a common virus may be involved in the genesis of breast cancer [150].

A possible viral candidate is the Epstein–Barr virus (EBV), which is a ubiquitous human γ herpesvirus that infects and establishes a mostly asymptomatic life-long infection in B lymphocytes [151, 152]. The data on breast cancer show interesting similarities to those data for Hodgkin's disease (HD) of young adulthood. First, the incidence of both neoplasms is higher in economically developed countries and is positively associated with higher socioeconomic status. Second, parity and early age at first full-term birth, as the result of relative immunosuppression during pregnancy, have been found to produce a significant reduction in risk of these neoplasms. Third, immunosuppressive conditions, which are associated with pregnancy, appear to lower subsequent breast cancer risk. Prolonged immunostimulation (pattern of EBV antibody titers) had been noted to precede the diagnosis of HD. Fourth, Reed–Sternberg cells, a distinctive cell in HD, has been observed in a large number of breast carcinomas in the absence of HD. Finally, the EBV genome has been detected in a subset of tumor specimens of breast cancer, as well as those of HD, although not consistently. In a study by Yasui and colleagues based on a population-based case-control study of breast cancer in women, aged 50–64, it was noted that those who reported a history of infectious mononucleosis relative to those who did not, had an increased risk for breast cancer [153]. Adjusting for confounders did not change this association [153].

Another viral candidate is the mouse mammary tumor virus (MMTV). In one study, MMTV-like envelope protein gene sequences were detected in 37% of human breast tumors, but not in normal breast tissue [154].

It appears that future research involving potential viral etiologies of breast cancer should be considered. Furthermore, vaccines may be used to prevent or modify the primary infection to reduce breast cancer risk.

Interpretation

Table 1 summarizes the consensus of evidence related to the environmental risk factors that have been thought to potentially influence breast cancer risk, as reviewed above. Based on this consensus, it appears that the majority of environmental exposures discussed in this review either exist at concentrations too low or have carcinogenic potential too weak to be easily identified as factors that influence the development of breast cancer, other than ionizing radiation. Therefore modifying factors that make some women susceptible to these factors and/or their combinations must be identified to assess the role that they play in the development of breast cancer. The context of the exposure assessments that create or influence susceptibility to breast cancer can be divided into three broad categories; timing of the exposure, environment and environment interactions, and environment and gene interactions.

Timing of environmental exposures

The biological sequence of events leading to breast cancer likely coincides with certain times of vulnerability during life. Much epidemiological and experimental evidence suggests the need to investigate the association of mutagenic or estrogenic chemical exposures that occur early in a woman's life, even *in utero*, with breast cancer risk [13, 155]. Studies of breast cancer suggest that the intrauterine environment, age at menarche, and age at first full-term birth, as well as the interval between these latter two events may be critical periods in the development of breast cancer [156]. This may be because the breast cells are undergoing longer uninterrupted intervals of differentiation and proliferation compared with later time periods in the lifecycle, and as a result are more vulnerable to carcinogenic exposure [157]. Experimental research has established that tumor initiation is more likely to occur during early breast development [158–161]. In addition, laboratory studies have found that chemical prenatal exposures can alter ductal and lobular development within the breast [162].

Table 1. Summary of scientific evidence for environmental factors that Influence breast cancer risk

Risk factors	Evidence
OCs	Results from studies of total PCBs[a], DDE[b], DDT[c], and other OCs (primarily pesticides) were for the most part null Studies reporting PCB congener-specific analyses were inconsistent
Organic solvents and other chemicals	As a whole, organic solvents and chemicals lacked association with breast cancer risk
Metals	Evidence emerging from epidemiological and rodent studies indicate a need for further investigation in humans
Ionizing radiation	Well known risk factor for breast cancer
Cosmic radiation	Studies suggest increased breast cancer risk among flight attendants, but the role played by cosmic radiation is unclear
Electromagnetic fields	No solid evidence for a link with breast cancer
Circadian rhythm disruption	Although studies suggest a link with breast cancer, there have been too few studies to be conclusive
Tobacco smoke	Recent studies suggest increased breast cancer risk with passive cigarette smoking Recent research suggests increased breast cancer risk with cigarette smoking during pregnancy
Viral infection	There is some support for the hypothesis that delayed primary EBV[d] infection may contribute to increased breast cancer risk
Protective factors	
Solar radiation	Studies indicate a protective effect for breast cancer

[a] Polychlorinated biphenyls.
[b] Dichlorodiphenyldichloroethane.
[c] Dichlorodiphenyltrichloroethane.
[d] Epstein–Barr virus.

In animals, a large number of exposures to phytoestrogens and synthetic estrogens may alter the onset of puberty [163, 164]. It has been noted that among girls exposed to higher versus lower levels of PCBs *in utero* experience an earlier age at menarche [165]. In addition, Rogan and colleagues observed a shortened duration of lactation among women with the highest exposures to DDE [166, 167]. These findings emphasize the need to pursue more research to identify environmental exposure experiences in early life that may affect breast cancer risk.

Environment and environment interactions

Mammary carcinogens may interact with other environmental exposures to increase risk beyond the risk associated with each individual exposure. Combinations of environmental exposures have not been well studied because of biological, as well as epidemiological study design complexities. A major obstacle of the study of joint exposures is the need for large numbers of participants with complete breast cancer related risk factor assessments.

Many *in vitro* studies have found the effects of environmental carcinogens to be additive [168, 169]. Environmental factor interaction may also occur between exposures of very different origins, such as chemical carcinogens and viruses. Solvents, DDT, dioxin, and PCBs are immunotoxic [170], and some of these chemicals have been implicated as cofactors in hematopoetic malignancies that may have a vital etiology, such as hairy cell leukemia [21, 171]. Similarly, recent studies suggest that tobacco functions as a cofactor to human papillomavirus infected cells, facilitating

neoplastic progression [172]. The examination of joint exposures of environmental carcinogens should also take into account other risk factors, such as BMI and alcohol intake that are known to affect endogenous hormone levels. For example, associations between OCs and breast cancer risk have been noted to differ according to BMI [173]. BMI has been reported to be associated with higher levels of circulating OCs in women [174–176]. In addition, alcohol intake has been associated with higher estrogen and androgen levels in women, especially among pre-menopausal women [177]. It is possible that women that have more of the risk factors associated with increased endogenous estrogen levels are more susceptible to the environmental carcinogens.

Environment and gene interactions

Because high penetrance genes, such as *BRCA*1 and *BRCA*2 and a few rare gene variants (*ATM*, *P*53, and *PTEN*) are estimated to account for only 5% of all breast cancers [178], a substantially higher proportion of breast cancer susceptibility may be determined by the interaction of low penetrance genes acting in concert with lifestyle and other environmental factors [179]. Thus, current efforts have been aimed at identifying mutations in low penetrance genes encoding for carcinogen metabolizing enzymes that are associated with increased rates of breast cancer. Examples of enzymes expressed in the human mammary gland that metabolically activate and/or detoxify environmental mutagens or estrogens are listed in Table 2 [180]. If detoxification of these carcinogens fails to occur, genetic mutations may result, some of which may not be repaired. Besides the involvement of the *BRCA* genes in DNA repair, the base excision repair gene, *XRCC*1, has been found to be associated with increased breast cancer risk [181]. *P*53 is best known as a tumor suppressor gene, but also has DNA repair functions [182].

Current evidence indicates that genetic variants in the metabolic pathways for the modulation of environmental carcinogens in combination with mutations in the DNA repair genes has been associated with acquired mutations in genes that suppress carcinogenesis (tumor suppressor genes). *P*53 is a tumor suppressor gene that encodes for a transcription factor involved with both the control of cell proliferation and apoptosis, and its inherited mutation causes the Li–Fraumeni syndrome, resulting in a breast cancer penetrance that approaches 100% for those who survive childhood [178]. *P*53 is overexpressed in approximately 40% of breast tumors, with approximately 20% having mutations in the gene [182]. Environmental carcinogens, such as the PAHs and ionizing radiation, have been linked to specific mutations along the *P*53 gene in breast cancer [182]. These mutations vary with ethnicity and geographical location, suggesting an environmental etiology for breast cancer [183].

Table 2. Examples of human carcinogen-metabolizing enzymes expressed in human breast tissue

Enzymes	Environmental carcinogens[a]
Cytochrome P450s	DMBA, PAHs, IQ, NNK, MeIQ, *N*-nitrosodialkylamines, Aflatoxin B1
N-acetyltransferases	*N*-OH-IQ, *N*-OH-PhIP, AAs
Epoxide hydrolase	PAHs
Glutathione-*S*-transferases	*N*-OH-PhIP
Sulfotransferases	*N*-OH-IQ, HAAs
Lipoxygenase	Aflatoxin B1, 4-aminobiphenyl

[a] Only published information on human enzymes is included: environmental carcinogen abbreviations: DMBA – 7-12-dimethylbenz[a]anthracene (a PAH); HAAs – heterocyclic aromatic amines; IQ – 2-amino-3-methylimidazo[4,5-*f*]quinoline (heterocyclic amine); MeIQ – 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (heterocyclic amine); *N*-OH-IQ – *N*-hydroxy-IQ; *N*-OH-PhIP – *N*-hydroxy-2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; AAs – aromatic amines; NNK – 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (tobacco nitrosamine); PAHs – polycyclic aromatic hydrocarbons.

Conclusions

Overall, experimental and epidemiological research suggests that environmental exposures and genetic pre-disposition in the context of the age at exposure and the hormonal milieu have a combined effect on breast cancer risk. The search for phenotypes and environmental exposure profiles associated with breast cancer appears to hold great promise for more precisely assessing breast cancer risks and developing breast cancer prevention interventions.

Thus, research designed to address innovative and emerging hypotheses that involve environmental factors may potentially advance our knowledge for the etiology of breast cancer. As a guiding principle, it makes sense to thoroughly investigate any environmental exposure that could follow a biologically plausible mechanistic pathway in the genesis of breast cancer. Related to this research, it will be important to

investigate new methodological approaches to assess carcinogen exposure (i.e., timing of the exposure, new biomarkers to assess exposure, and the development, and validation of new exposure assessments), as well as environment–environment and gene–environment interactions.

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