Is Breast Cancer an Environmental Disease?

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Introduction

Breast cancer is the most common malignancy in women, both in the developed and developing world. In U.S. women, it accounts for one-third of all cancer diagnoses and 15% of all cancer deaths: only lung cancer causes more cancer deaths. Based on the data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program, 30% of all incident cancers among women are due to breast cancer, which makes it the most commonly diagnosed cancer. The American Cancer Society estimated that 192,000 cases and 40,000 deaths would occur among U.S. women during 2001. Breast cancer is rare among men, with only 1,400 cases and 400 deaths estimated for the year 2000 in the U.S.[1]

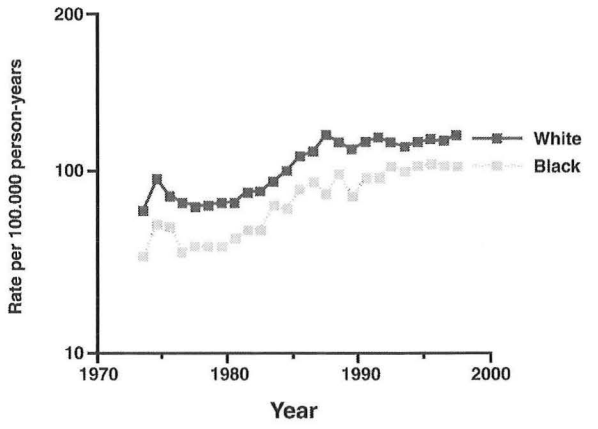
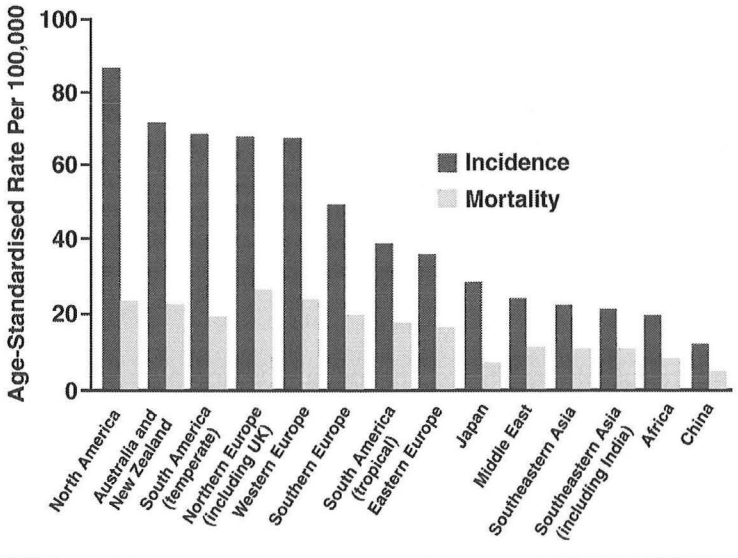


Figure 1. Age-adjusted (1970 U.S.) SEER incidence rates: female breast cancer (1973-1997). *Adapted from Lacey JV, Devesa SS, Brinton LA. Recent trends in breast cancer incidence and mortality. Environ Mol Mutagen 2002; 39:82-88.*[1]

Breast cancer incidence rates have continued to rise since the 1970s, which has been true for most countries world-wide. **Figure 1** reports the age-adjusted breast cancer incidence for the U.S. between 1973 and 1997. Increased mammogram screening may explain the documented jump in breast cancer rates during the mid-1980s. In addition, geographical differences in breast cancer rates exist, with high rates of disease in North America, Northern Europe, intermediate rates in South and Central America and Southern and Eastern Europe, and low rates in Africa and Asia (**Figure 2**).[1, 2] 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.

Figure 2. World-wide variation in breast cancer rates (data from the International Agency for research in Cancer 1990). *Adapted from Lacey JV, Devesa SS, Brinton LA. Recent trends in breast cancer incidence and mortality. Environ Mol Mutagen 2002; 39:82-88.*[1]



Female gender, age, and country of birth are the strongest determinants of breast cancer risk. The established risk factors for breast cancer are primarily the reproductive risk factors: early age at menarche, nulliparity, late age at first full-term pregnancy, late age at lactation and short duration, late menopause, and inheritance (e.g. *BRCA1* and *BRCA2* 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 an 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 U.S.[4, 5] It is estimated that another 1% of breast cancers in the U.S. may be attributable to diagnostic radiography.[6] Furthermore, we have not yet been able to identify the causes for the increasing incidence of breast cancer, and the geographical variation in its regional international incidence rates. As a result, greater attention has been focused on the environmental exposures, including some of the other known risk factors (radiation, exogenous estrogens, alcohol consumption, and higher educational level and socioeconomic status) that may be responsible for some portion of breast cancer incidence.

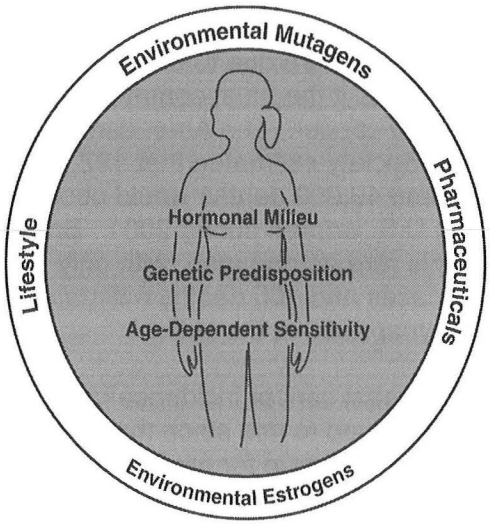


Figure 3. A complex interaction of internal and external factors leads to breast cancer. *Adapted from Pollner F. A holistic approach to breast cancer research. Env Health Persp 1993;101:116-120.*[9]

Studies of twins and of families with cancer in Sweden, Denmark, and Finland lend support to the idea that breast cancer risk has a strong environmental component. These studies indicated that greater than 60% of breast cancer has an environmental etiology.[7, 8] Most scientists now believe that breast cancer involves a complex interaction of internally and externally introduced factors, all played upon by the element of time (**Figure 3**).[9]

Breast Cancer Carcinogenesis and Environmental Influences

In 1700, Ramazzini discovered and reported on the increased risk of breast cancer among single women (nuns) compared with married women. This perceptive observation has now become recognized as the first association of cancer causation with occupation. Thus, the hypothesis proposed by Ramazzini was that the increased risk of breast cancer could be related to the absence of an active reproductive life, in particular, pregnancy and lactation.[10] A century later, well before estrogen was discovered, a Scottish surgeon, George Thomas Beatson, noted that breast cancer did not occur in women who had their ovaries removed.[11] Today we know that oopherectomy in women under the age of 30 effectively prevents breast cancer. Reducing estrogen levels overall slows breast cell proliferation and includes cell death or apoptosis.[11] Therefore, in the genesis of breast cancer it is thought that estrogen acts as a tumor promoter, by providing the stimulus for genetically altered breast cells to divide more rapidly than normal cells, a process that eventually causes a tumor.[12]

Cancer is considered to be the end-result of a multi-step process in which a large number of endogenous and exogenous factors interact, simultaneously or in sequence, to disrupt normal cell growth and division (**Figure 4**). Three distinct stages have been identified for carcinogenesis after exposure to a carcinogen: (1) initiation- normal cell to pre-cancerous cell, (2) promotion- pre-cancerous cell to cancer cell, and (3) progression- growth of the cancer cell into a tumor.[13] It is also well known that the tissue that is rapidly turning over is the most susceptible to malignant change.

Moogavkar, Day, and Stevens proposed a two-stage model for the tissue kinetics in the genesis of breast cancer (**Figure 5**), based on the multi-step biological model for carcinogenesis (**Figure 4**), to predict age-specific incidence curves of breast cancer.[14] This mathematical model was based on the hormonally determined evolution of breast tissue with age at menarche and at menopause, and the effect of pregnancy, particularly the first pregnancy, on the kinetics of breast tissue. They hypothesized that malignancies develop from undifferentiated stem cells, as a result of two independent events that occur during cell division. This epidemiological model for predicting breast cancer incidence (**Figure 5**) can be summarized as follows. A normal stem cell can either: (1) differentiate (die), and thus not be at further risk of potentially malignant transformation, (2) divide into two normal stem cells (each of which is at risk for malignant transformation), or (3) divide into a normal stem cell and one initiated cell, which is the first event in malignant transformation. After the first event in malignant transformation, initiated cells can differentiate and thus be removed for the pool of cells at risk for further malignant transformation, (2) divide into two initiated cells, or (3) divide into one initiated and one pre-cancerous cell. The pre- cancerous cell grows into a tumor. An event may be viewed as the cumulative effect on a cell of tumor initiator/s. Tumor promoter/s, on the other hand, would act by enhancing normal proliferation of the stem and initiated cells. The mathematical explanation of this model assigns different values to the net cell growth constants for the cells (stem, initiated, and pre- cancerous) before and after menopause, and different values for the probabilities of the events in different populations.

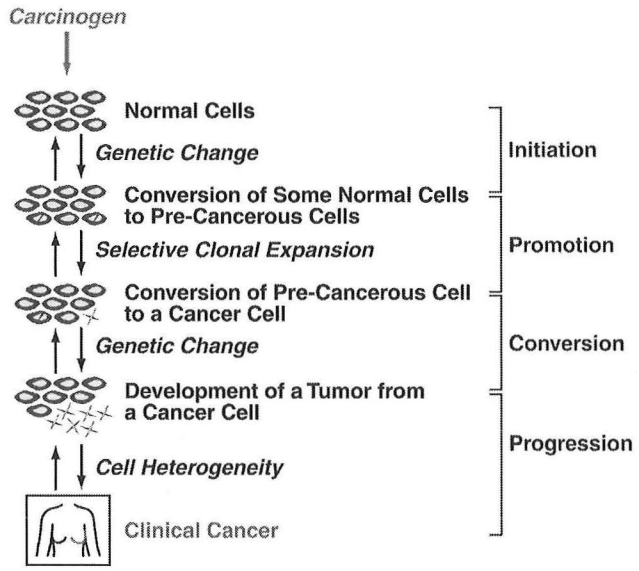


Figure 4. The biological model for carcinogenesis at the cellular level.

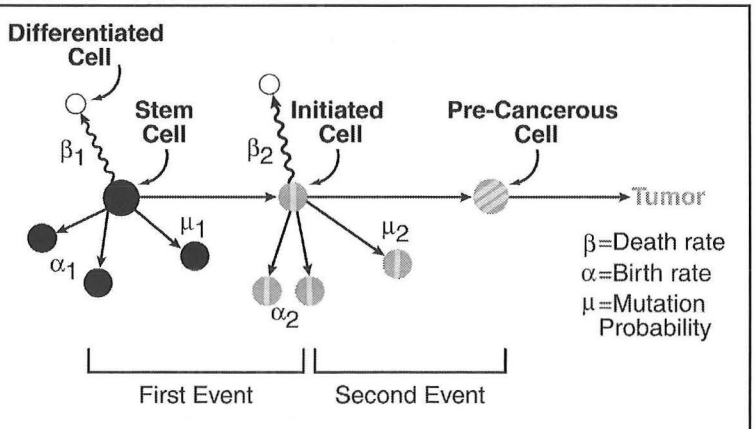


Figure 5. A two-stage kinetic model for breast carcinogenesis at the cellular level. *Adapted from Moolgavkar SH, Day NE, Stevens RG. Two-stage model or carcinogenesis: epidemiology of breast cancer in females. JNCI 1980;65:559-569.*[14]

The model by Moolgavkar, Day, and Stevens (**Figure 5**) accurately simulated the age-incidence curves for breast cancer in six populations over 30-40 years (**Figure 6**).[14] This model also accurately simulated the inverse relationship between age at birth of first child and the risk of breast cancer, during which time there is breast tissue proliferation during the pregnancy and then marked differentiation of the mammary epithelial cells after childbirth. The earlier in life that this happens, the

shorter would be the time when large numbers of undifferentiated susceptible cells (stem and initiated cells) are present in the breast, and the lower would be the risk for breast cancer. Likewise, the model simulates the risk for breast cancer associated with early age at menarche and late age at menopause, since there would be a longer period of time that a large number of stem and initiated cells were present in the breast tissue. The model has added value in that it can be used to estimate the amount of geographic variance in breast cancer incidence rates that may be due to environmentally derived exposures.

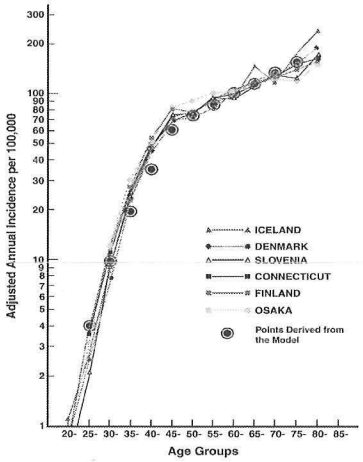


Figure 6. Age-specific incidence curves of breast cancer in different populations after adjustment for temporal trends, and the shape of the incidence curve generated by the model. *Note* incidence is on a logarithmic scale. *Adapted from Moolgavkar SH, Day NE, Stevens RG. Two-stage model or carcinogenesis: epidemiology of breast cancer in females. JNCI 1980;65:559-569.*[14]

Environmental Chemical Exposures Relevant for Breast Cancer Etiology

The National Toxicity Program has studied the potential of 500 environmental chemicals, including pharmaceuticals, in controlled rodents studies.[15, 16] Based on these studies, a number of potential breast carcinogens for humans have been identified. Some of these carcinogens are also known environmental contaminants and commonly used pharmaceuticals (**Table 1**). Chemicals that are risk factors causally associated or possibly associated with breast cancer in humans are listed in **Table 2**. 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 the known environmental contaminants are more likely to be encountered in an industrial environment than in settings that women experience daily. However, in a recent survey, 86 potential mammary gland toxins were identified and measured in the household dust and air, including 9 mammary carcinogens and 77 hormonally active agents or closely related compounds. Of these, greater than 30% were detected at least once in a pilot study for 3 homes.[18]

Table 1. Known Mammary Gland Carcinogens in Rodents

Environmental Contaminants
- Benzene- *solvent*
- Butadiene- *rubber manufacturing*
- Dioxins- *byproducts of combustion or herbicides*
- 1,2 Dichloropropane- *solvent in dry cleaning*
- Methylene Chloride- *solvent*
- Sullfalte- *herbicide*

Pharmaceuticals
- Antidepressants (esp. SSRIs*)
- Estradiol
- Furosemide
- Isoniazid
- Indomethacin
- Metranidazole
- Phenacetin

*Selective serotonin re-uptake inhibitors.

Many of the environmental chemicals currently being used are analogs of known mammary gland carcinogens for rodents (**Table 1**). Other chemicals (dichlorodiphenyltrichloroethane [DDT], polychorinated biphenyls [PCBs], and atrazine) that are not causally associated with breast cancer in rodents or humans are known to enhance or inhibit tumor growth.[19, 20] The organochlorines (OCs), including DDT, PCBs, dioxin, polybrominated biphenyls (PBBs), and phenoxy acids as well as solvents, may reduce cell-mediated immune function.[21] A number of environmental chemicals have been investigated in epidemiological studies with respect to

Table 2. Chemicals Associated with Breast Cancer in Humans*

Alcohol
Diethylstilbesterol
Hormone replacement therapy
  Estrogen
  Estrogen and progesterone
Estrogens
  Steroidal
  Nonsteroidal
Oral contraceptives (combined estrogen and progesterone

Based on data presented in Key, Verkasalo, and Banks.[3]

their potential influence on breast cancer risk.

Occupational Studies

Occupational exposure to environmental chemicals usually are 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. Some of the studies that have investigated the incidence or mortality of breast cancer in specific occupations support an environmental etiology for this disease. **Table 3** lists the occupations that have been linked with breast cancer risk by at least one study (administrative, case-control or cohort studies).[22] Evidence that chemical exposures may increase the risk for breast cancer incidence or mortality has been most consistent among teachers and managerial personnel. However, it is not obvious that these jobs would have high carcinogenic exposures.

Table 3. Occupations Linked with Breast Cancer

White collar managerial occupations & other related professions
Clerical & related jobs
Teachers
Scientists
Nurses
Other health professionals
Clergy
Cosmetologists, beauticians
Pharmaceutical industry
Textile & clothing workers
Bartenders & waitresses
Furniture workers
Transportation industry
Electronics manufacturing
Printing
Farmers, agriculture
Shoe & leather
xRay technicians, radiation workers
Laundry & dry cleaning
Rubber workers
Asbestos
Chemical industry (excluding petroleum manufacturing)
Potential exposure to extremely low frequency electromagnetic fields

There have been many limitations to the occupational studies, as reviewed by Goldberg and Labreche.[22] Of primary concern for many of these studies were the imprecise or poorly classified exposures or disease status, the examination of breast cancer mortality rather than incidence, and the lack of information regarding confounders, such as the reproductive risk factors for breast cancer. Furthermore, 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. Either situation reduces statistical power to examine hypotheses. Furthermore, poor assessment of exposure or disease is likely to result in attenuated risk estimates, whereas failure to consider confounders can overestimate or underestimate study findings. Finally, conclusions drawn from mortality studies of breast cancer often can be misleading with regard to understanding etiology because the women who survive the disease are excluded. However, this type of research may be useful for directing more carefully designed analytical studies.

Organochlorine Exposure

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 is the pesticide DDT, which was introduced in the U.S. in 1945.[23] DDT was used widely in the U.S. for insect control in forestry, agriculture, and building protection from 1945 until the early 1960s. The use of DDT peaked in the U.S. in the early 1960s and was banned in 1972.[23] PCBs were extensively used

in the U.S. as dielectric fluids in transformers and capacitors, as plasticizers, lubricants, and heat transfer fluids, and in the manufacture of such products, such as paints and paper until their use was discontinued in 1977. Dioxins are also OCs that are reproduced as combustion byproducts for industrial processes or as contaminants of herbicides. Other OCs include pesticides used in lesser amounts, such as lindane and hexachlorobenzene. The biological basis for linking these exposure to breast cancer involves their considerable use and use patterns, their persistence, their potential to act as endocrine disruptors, and their carcinogenicity in animals. Many OCs, including its metabolite, dichlorodiphenyldichloroehtylene (DDE), and some PCBs, are considered endocrine disruptors because they are weakly estrogenic or antiestrogenic in experimental assays.[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 DDE, the major metabolite of DDT, and PCBs. Levels of DDT, DDE, and PCBs detected in food and in human blood and tissue has declined since their discontinuation in 1972. 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[28] 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. Before 1993, the possible association between adipose tissue or blood OC levels and breast cancer had been examined in only a few small studies, most of which examined OCs 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, there have been nearly 30 published studies that have attempted to replicate its results. With rare exceptions,[29-33] there is consistent evidence from many methodologically sound studies of no association between levels of persistent OC compounds, notably DDE and PCBs, and breast cancer. 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 U.S., Canada, Europe, and elsewhere. [34-60]

Many studies have been conducted in the U.S. to address the possibility that exposure to OCs may explain the higher rates of breast cancer observed there.[37, 38, 40, 42, 46, 49, 57] 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 1,400 cases from 5 of these studies found no increased risk of breast cancer with exposure to OCs when adjusted for race.[61] Therefore, exposure to DDT and PCBs, as experienced by women in these studies, does not appear to explain regional differences in breast cancer rates.

Only one study to date has looked at age dependent OC exposure and breast cancer risk.[32] 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 premenarchal. Although the number of breast cancer cases in this study

were 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 the hypothesis in subgroups of women defined by race, menopausal status, history of parity and breastfeeding, body mass, tumor characteristics, and genetic factors. No consistent subgroup findings have emerged. However, results from one study found an increased risk of breast cancer associated with higher than average serum PCB levels among women with the Cytochrome P450A1 genotype (CYPA1).[62] Cytochrome P450 mediates the metabolism of some PCBs, which have been associated with greater toxicological activity.[63]

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.[50] Unfortunately, the PCB congeners with the highest potential estrogenicity are more quickly metabolized.[64] 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 at 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, based on studies that involved women that survived the atomic bombings or had undergone other medical therapy involving large does of ionizing radiation.[65-67] Future follow-ups of the Svesco, 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.[68] Except for one study, none of the studies that used woman with BBD as controls found a positive relationship between levels of OCs and breast cancer risk.[29]

Other Environmental Chemical Exposures

Certain organic solvents have been reported to be carcinogens in animals and some are mammary gland 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. Several analytic epidemiological studies have been published on the solvent related jobs related to the incidence of breast cancer. Most of these studies have not shown a significantly increased risk for breast cancer, however several have suggested positive associations for breast cancer risk.

The laundry and dry cleaning industry has used several organic solvents over the years, with tetrachloroethylene being the most prevalently used nowadays.[69] Only one case-control study has been conducted to date that assessed breast cancer risk with this occupational

exposure, finding 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 five years in the coiling and wire drawing department; methylene chloride and trichloroethylene were the solvents used.[71] 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.[72] Again, 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.[73] However, in a Swedish cohort study of oil refinery workers adjusted only for age, an increased risk for breast cancer incidence was noted.[74]

A population-based case-control study in the state of Washington, adjusted for age, parity, education, and alcohol intake reported a nonsignificant increase in breast cancer incidence among females in the occupational group of painters, sculptors and printmakers.[75] In a population-based case-control study that involved 4 states in the U.S. (Maine, Massachusetts, New Hampshire, and Wisconsin), adjusted for state, age, reproductive factors (menopausal status, age at menarche, parity, age at first birth, and lactation history), family history of breast cancer, BBD, education, body mass index (BMI) and alcohol consumption, was associated with a nonsignificant increase in breast cancer risk among women working in the precision production jobs.[76]

A few ecological studies have assessed the risk of breast cancer with environmental exposures from organic chemicals, although some initial associations subsequently have been suggested to be the result of confounding factors.[77] 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.[78] A study of women on Long Island, New York, in which the addresses 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 postmenopausal women living closer to the sources of exposure.[79] In Massachusetts, case-control studies of breast cancer have investigated tetrachlorethylene contamination of municipal water supplies; there were suggestions of positive associations with breast cancer risk.[80]

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 solvent are short-lived in the body), collectively these studies suggest positive associations between organic solvent exposures and breast cancer risk.

Pharmaceuticals

Many of the commonly used pharmaceuticals have been shown to cause mammary gland cancer in rodents (**Table 1**). However, the relationship between exposures to these chemicals and breast cancer development has not been studied until recently. Most of this research has focused on the antidepressants. Antidepressants have been available since the 1950s, and their use has been widespread. Whereas, in the first three decades most antidepressant medications were tricyclics (such as amitriptyline), within the past 15 years

selective serotonin re-uptake inhibitors (SSRIs), such as Prozac and paroxetine, have become much more popular. In the early 1990s, animal studies of anti-depressant exposure demonstrated increased mammary gland tumors in some rodents.[81, 82] At least three potential mechanisms for human breast cancer have been postulated: selective uptake inhibition itself, stimulation of prolactin secretion, and inhibition of the action of various cytochrome P450 enzymes.

Few epidemiologic studies of breast cancer risk after exposure to pharmaceuticals have been conducted. One small case-control study showed a small nonsignificant increase in breast cancer risk for all antidepressants combined.[83] A large surveillance study of many prescription drugs found no increased breast cancer risk,[84, 85] and a large study in California that investigated the association of 200 prescription drugs with the risk for breast cancer was also negative.[86]

Two large case-control studies and one smaller case-control study of pharmaceutical exposure and breast cancer risk have been published recently. In one, 5814 women with primary breast cancer were compared to 5095 women with primary malignancies at other sites, and to 5814 women with other chronic medical conditions, where lifetime medication history was collected by interview.[87] Antidepressants, phenothiazines, and antihistamines were generally associated with no increased risk, while a significantly elevated risk was apparent for the selective SSRIs. In the second case-control study, 701 registry-identified primary breast cancer cases aged 25-74 years were compared to 702 population controls of similar age.[88] Medication history was collected by mailed questionnaire. While only 10.3% of the cases and 8.7% of the controls ever used antidepressants, use of tricyclic drugs for more than two years showed a two-fold nonsignificant increased risk for breast cancer. Of note is the higher increased risk for the SSRI medication paroxetine (odds ratio [OR] 7.2, 95% confidence interval [CI]: 0.9-58.3), one of six most commonly reported antidepressants, although this result may be a chance finding given the large number of medications examined. The third study was of a very similar design, with 2681 (74% response) breast cancer cases compared to 2677 (64% response) population controls.[89] Daily use of all antidepressants combined for two or more months was associated with a slightly increased breast cancer risk (OR 1.3, 95% CI: 1.1-1.5). The SSRIs were associated with the highest breast cancer risk (OR 1.5, 95% CI: 1.2-2.0).

Other Environmental Exposures Relevant for Breast Cancer Etiology and Progression

Radiation

Ionizing

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.[65-67] 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 had 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 1.4-2.2-fold increased risk for developing cancer.[90] Women irradiated as treatment for postpartum mastitis were found to have a two-fold risk for developing breast cancer as compared to cohort-control, non-irradiated mastitis patients and non-irradiated sister controls.[91, 92] 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.[93, 94] 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.[95] The majority studies of workers exposed to low levels of radiation, such as weapons facilities, over an extended period of time, have not reported an increased breast cancer risk even in the higher ranges for such exposures.[22] It is possible that these studies had methodological problems, such as those discussed above for the occupational studies related to environmental chemical exposures.

Cosmic

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 greater biologic effectiveness than gamma radiation. However, there are few available data on the carcinogenic effect of neutrons in humans.[96] There were increases in breast cancer incidence and mortality among flight attendants in one cohort study (n= 1690 with 1532 women)[97] and in a record linkage study (n= 1764 with 1577 women),[98]but not in another cohort study (n=20551 with 16014 women).[99] 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, i.e. cosmic radiation, disturbance of circadian rhythm, and electromagnetic force (EMF), or a combination of these factors is still a puzzle, as the confounding due to parity was ruled out in one of these studies.[97]

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.[100] 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 gland tumors in the exposed rodents compared to their controls. Changes in serum prolactin and estrogenic levels were noted in the light-exposed animals. [101]

In several studies of male breast cancer, an elevated risk was observed among men employed in either electrical,[102, 103] telephone,[104]or railroad[105] 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,[106-108] most do not, as reviewed by Caplan and colleagues.[109] Furthermore, the inconsistent findings for studies examining other sources of EMF exposure, such as residential proximity to power lines[110-117] or electric blanket use,[118-122] do not appear to corroborate a harmful relationship between EMF exposure and breast cancer risk. A major methodological issue for these studies were difficulties assessing 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.[123-126] An inverse relationship of colon cancer with exposure to mean daily solar radiation (an indirect measure of ultraviolet-B which can create 25-hydroxy-vitamin D in the skin)

has been observed.[127] In addition, a 19-year prospective cohort study found that dietary vitamin D and calcium reduced the incidence of colon cancer.[128] Based on scientific evidence that vitamin D is thought to play 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 (sulfur dioxide and ultraviolet-light-blocking aerosols) was examined. This study found that there was a statistically significant and positive association between these two measures of air pollution and age-adjusted mortality rates for colon cancer in women and men, and breast cancer in women.[129] These findings were duplicated in an ecological study conducted in the U.S.[130] and the former Soviet Union.[131]A recent ecological study, conducted by Grant using breast cancer mortality rates from 1989-1996, for 35 countries (include developed Western countries) found a negative association of breast cancer mortality rates with solar ultraviolet-B radiation.[132] 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 U.S. regions of high solar radiation.[33]

Circadian Rhythm Disruption

As mentioned above, 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.[100, 101] 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.[134] 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.[135] These studies indicate that it is necessary to further explore the relationship between light exposure and cancer risk through the melatonin pathway.

Cigarette Smoking

Cigarette smoking is not an acknowledged breast cancer risk factor, but there has been continued work in this area because chemicals in cigarette smoke are potent mammary gland carcinogens in rodents and are human carcinogens for other organs (e.g., lung, bladder, and lymphatic system).[136] Experimental studies have indicated that tobacco smoke contains potential human breast carcinogens (polyaromatic hydrocarbons [PAHs] , heterocyclic aromatic amines [HAA], and N-nitrosamines),[137-140]and a higher prevalence of DNA adducts and *P*53 gene mutations found in breast tissue for smokers compared with nonsmokers.[141-147]

The majority of the epidemiological studies to date examining smoking alone as a breast cancer risk factor do not support an overall association, based on recent reviews.[148, 149] These studies have included case-control (screening, hospital or population-based) and cohort study designs. Major concerns for these studies, were exposure misclassification and loss to follow-up.

It is thought that failure to detect an association may be due to the fact that tobacco smoke has been hypothesized to have dual influences on breast cancer risk. It may increase risk by either acting directly as a genotoxic agent or by acting as a promoter, but may reduce its risk through its anti-estrogenic properties.[150-152] These anti-estrogenic properties have been suggested since studies have shown that smoking is associated with an increased risk for osteoporosis,[153, 154] an earlier age at natural menopause,[152]and attenuated effects of hormone

replacement therapy.[154] This risk may also be dependent on the age of the individual or the time period of exposure to tobacco smoke.[155] Animal and in vitro studies strongly support the idea that mammary gland cells at an early age of development are more susceptible to PAH-induced tumorogenesis.[156-158] Epidemiological studies that have investigated this question have found trends toward elevated breast cancer risk among women who report smoking as teenagers,[136, 159] as well as women exposed to passive smoke at younger ages,[155] or who actively smoked during their first pregnancy.[160] However, in a case control study nested within the Nurse's Health Study cohort, a positive association with smoking before a first-term pregnancy and breast cancer risk was not found.[161] Likewise, in a recent population-based case-control study by Kropp and Chang-Claude that in involved 468 premenopausal breast cancer patients and 1093 controls, it was noted that exposure to environmental tobacco smoke during childhood or before the first pregnancy did not appear to increase breast cancer risk. However, former (OR, 95% CI 0.8, 1.7) current smokers, (OR 1.5, 95% CI: 1.0, 2.2) ever active smokers (OR 1.3, 95% CI: 0.9, 1.9), ever passive smoking (OR 1.6, 95% CI: 1.1, 2.4), and passive and active smoking (OR 1.8, 95% CI: 1.2, 2.7) had increased breast cancer risk.[162] The unexpected similar odds ratio with ever passive smoking as compared with current smoking was hypothesized to be due to that fact that passive smoke contains higher concentrations of smoke related carcinogens as compared with active smoke. In addition, active smoke has been associated with an antiestrogenic effect not thought to be present in passive smoke, which may reduce the carcinogenic potential of its constituents.[162]

The carcinogenic effects of compounds found in tobacco smoke have been hypothesized to be stronger or weaker according to genotypes that either biologically activate or detoxify these compounds in the human body.[140] Thus cancer risk is, at least in part, an integrated function of carcinogen exposure and polymorphisms in genes involved in carcinogen metabolism.[163] However, there is still too few data to evaluate the strength, consistency, and dose-dependent nature of the association between cigarette smoking and breast cancer risk related to gene variants involved in carcinogen metabolism and DNA repair.

Mutations in the *P*53 tumor suppressor gene, which are found in 15-30% of breast cancer,[164] may be another biological marker of cancer risk that can be linked to smoking-specific carcinogens. More specifically, distinct patterns of *P*53 "mutation spectra" (transversion, transitions, deletions, and insertions) may be linked to certain carcinogenic exposures. In the Carolina Breast Cancer Study (population-based case control study),[152] an increased prevalence and altered spectrum of *P*53 mutations in breast tumors were observed among current smokers compared with never smokers; thus smoking may be associated with genetic damage in breast epithelium. It is noteworthy that the breast tumors with the most pronounced smoking-related mutational pattern were from women who had smoked for more than 20 years, although total *P*53 mutations were not associated with smoking duration. However, in another U.S. population-based case-control study,[165]current cigarette smoking was associated with a statistically nonsignificant increased risk of breast cancers that were positive for the *P*53 protein expression by immunohistochemistry, but not with cancers that were negative for *P*53 protein expression.

In summary, the association between cigarette smoking and breast cancer risk remains unclear. Recent findings of the increased risk with smoking of longer duration, smoking before a first term pregnancy, and passive smoking require confirmation in future epidemiological studies, as do suggestions of increased risk among women with certain genotypes. In addition, more laboratory studies are needed to investigate the molecular mechanisms underlying the effect of cigarette smoking on breast cancer risk.

Diet

In experiments in animals, conducted greater than 50 years ago, diets high in fat increased susceptibility to mammary gland tumors in rodents.[166] In the 1970s, an ecological study found a strong positive correlation was reported between estimates of national per capita consumption and national incidence and mortality rates for breast cancer.[167] However, even with the *ecological fallacy*- that we may be ascribing to members of a group characteristics that they do not possess as individuals, [168] this study had methodological issues. These issues were that the quality of the data on national per capita fat consumption was in question[169], and at least part of the apparent correlation was due to a higher prevalence of the reproductive risk factors for breast cancer in countries with the higher fat consumption.[170-172] A short time later, the largest case-control study that studied this relationship (n = 2024 cases), found no appreciable difference in fat intake between the cases and controls.[173] To overcome a possible sample size issue, the data from 12 other case control studies (n = 4312) were pooled and analyzed, indicating that there was a significant positive association between total- and saturated-fat intake and the risk of breast cancer.[174] However, these results were still thought to be preliminary because case-control studies can be susceptible to recall and selection bias that can lead to spurious associations.[175] Subsequently, the results of several large cohort studies of fat intake and breast were found to be variable.[176] The possible limitations of these studies were thought to be chance, error in assessing diet, the use of various ranges of fat intake, and the difference in the statistical analyses. To mitigate some of these factors, a pooled analysis of seven prospective cohort studies was performed, showing that there was no association between fat intake and breast cancer risk in adult women in the more developed countries.[177] However, these results may not entirely explain an effect of fat on breast cancer, because few women are likely to have a very low fat intake in the long-term and because there is considerable error in the measurement of fat intake using dietary questionnaires; study participants may have a substantially higher fat intake than they report.

More recent studies have looked at other possible dietary determinants of risk, such as the consumption of meat, fiber, fruit and vegetables, and plant estrogens (phyto-estrogens). There may be a moderate protective effect for a high consumption of vegetables,[178] but results for meat, fiber, and fruit have been inconsistent, and breast cancer risk has not been shown to be lower in vegetarians as compared to non-vegetarians in the developed countries.[179] Although there is now enthusiasm for studying the soy products, a source of phyto-estrogens, because they are hypothesized to block effects of the more important endogenous estrogens and thereby reduce breast cancer risk, the results of these studies either were null or showed non-significant decreases in breast cancer risk associated with the consumption of soy products.[180-186]

Alcohol

The association of alcohol consumption with increased risk for breast cancer has been a consistent finding in the majority of the epidemiological studies over the last 20 years.[187] The effect is modest and cannot be explained by any other known risk factors. Collectively, these studies have shown that alcohol consumption is associated with a modest increase in the risk of breast cancer; risk increases by roughly 10% per 10 grams of alcohol consumed per day.[188] Within the range of light to moderate alcohol intake, breast cancer risk seems to increase linearly, so an intake of around 30 grams of alcohol per day is associated with about a 30% increase in breast cancer risk (**Figure 7**). Interestingly, studies have not shown higher risks at higher consumption or among women with alcoholism.

Evidence from laboratory human and animal studies support plausible biological mechanisms for the positive association between alcohol consumption and breast cancer risk noted with the epidemiological studies, such as increased circulating estrogens and androgens, enhancement of the mammary gland susceptibility to carcinogenesis, and increased mammary gland carcinogen DNA damage. Whether diet and hormones modify the association of alcohol with breast cancer is of considerable interest.

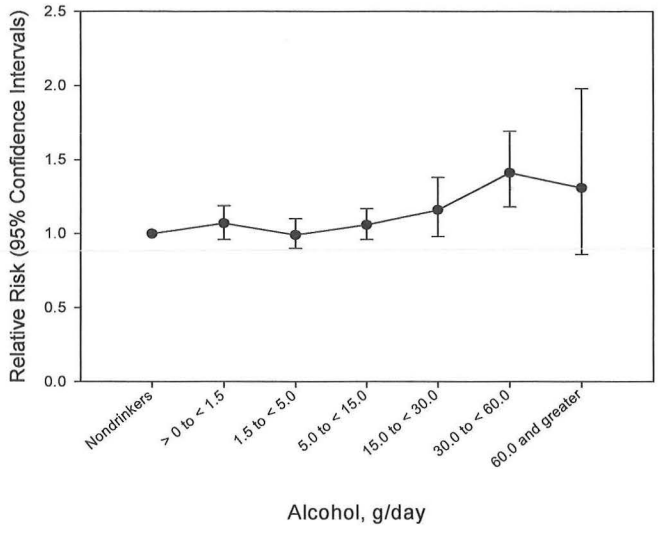


Figure 7. Relationship between alcohol intake and breast cancer risk. *Data adapted from Smith-Warner SA, Spiegleman D, and Yaun S-S, et al.).*[200]

Zhang and colleagues reported that women consuming more than 15 grams of alcohol per day and whose intake of folate was less than 300 micrograms per day had a higher relative risk for breast cancer, compared with women consuming the same level of alcohol along with folate levels greater than 300 micrograms per day.[189] Other reports[190-192] confirm this relationship. Furthermore, low-to-moderate alcohol consumption, in contrast to heavy drinking, may not necessarily result in folate depletion.[193-196] Yet, in combination with low folate intake, ethanol and/or its primary metabolite acetaldehyde may alter folate or methionine metabolism so that an imbalance in DNA methylation or in DNA damage/repair processes could lead to DNA instability or inappropriate gene expression.[197, 198] Alcohol consumption also has been associated with decreased blood levels of β-carotene, lutein/zeaxanthin, and vitamin C, which are thought to be cancer protective.[199, 200] Taken altogether, these studies suggest that alcohol consumption, especially at higher levels, may be associated with increased breast cancer risk, in part because of the negative impact of alcohol intake on the dietary factors that are thought to be cancer-protective.

Five out of 6 published studies suggest that alcohol is associated with mammagraphically dense breast tissue.[201-206] These dense patterns of breast tissue are associated with atypical hyperplasia and/or carcinoma insitu[207] and with cytological atypia in nipple aspirates,[208] which may be the result of enhanced mutagenesis in the breast.[209] Related to this noted phenomenon, is a recent report that mammographic density is positively associated with plasma insulin-like growth factor I (IGF-I) levels and inversely associated with plasma IGF binding protein 3 (IGFBP-3) in premenopausal women,[210] which warrants further evaluation.

Exogenous Estrogens

The use of diethylstilbesterol during pregnancy is now banned, but studies of women exposed from the 1940s to the 1960s show that such use was associated with a 30% increase in the subsequent risk of breast cancer in the women who were treated.[211]

Studies indicate the breast cancer is increased by around 25% in current users of combined oral contraceptives, but the excess rate falls after cessation of use. It has been shown that 10 years or more after use stops that no significant increase in risk is evident.[212]

Use of hormonal therapy for menopause occurs at a time when a woman is at high and increasing background risk for breast cancer. Data analyzed by the Collaborative Group on Hormonal factors in Breast Cancer and another large study have shown that among current users of hormonal therapy, the risk of breast cancer increases with increasing duration of use and that this excess decreases after cessation of use.[213, 214] Most studies so far suggest that five or more years after cessation of use of hormonal therapy for the menopause, there is no significant excess of breast cancer relative to never users. The magnitude of the effect of hormonal replacement therapy for the menopause on breast cancer risk is the subject of ongoing debate. Most of the studies so far relate to use of preparations containing estrogen alone, and the data for the studies analyzed by the Collaborative Group show that, among current and recent users, use of hormonal therapy for about 10 years increases the risk of breast cancer by roughly 35%; the risk of combined estrogen and progesterone was slightly larger but was based on less data.[213] However, most studies suggest that the use of combined estrogen and progesterone preparations increase the risk of breast cancer more than the use of estrogen alone.[213, 214-216]

Food By-Products and Food Additives

PAH and HAA compounds, although the putative carcinogens in cigarette smoke, are also present in foods cooked at high temperature, smoked foods, and charbroiled meats. HAA exposures may be derived predominantly from cooked meat. 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP), the major HAA compound found in the Western diet, has been shown to induce cancer in the mammary gland of rats.[217, 218] A number of recent studies have examined relations between the intake of cooked meat and breast cancer risk; some[219, 220] but not all[221, 222] studies reported significant associations.

In the U.S., the 1958 Food Additives Amendment to the Federal Food, Drug and Cosmetic Act of 1038 requires that food manufacturers to demonstrate the safety of food additives to the Food and Drug Administration (FDA). The amendment contains a provision that prohibits approval of a food additive if it is found to cause cancer in humans or animals.[223] Even though there are some disagreements, it is thought that foodborne carcinogenic risk probably overwhelmingly originates from the food itself and not from food additives, pesticides, or other environmental contaminants.

Air Pollution

PAHs are produced during combustion and are found in polluted air. However, research related to breast cancer risk and PAHs and other potentially carcinogenic byproducts of combustion has not been done.

Viral Infection

Investigating viruses as possible etiologic factors for several disease has regained popularity recently. One hypothesis suggests that late exposure to a common virus may be involved in the genesis of breast cancer.[224]

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.[225, 226] The data on breast cancer show intriguing similarities to those data for Hodgkin 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 birth have been found to produce an appreciable reduction in risk of these neoplasms. Third, immunosuppressive conditions, which is 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 necessary but not sufficient diagnostic characteristic of HD, has been observed in an appreciable 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 middle-aged women, it was noted that women that reported a history of infectious mononucleosis, relative to women who did not, had an increased risk for breast cancer.[227] Adjusting for confounders did not change this association.

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.[228]

Future research involving potential viral etiologies of breast cancer should be considered, since vaccines can be used to prevent or modify the primary infection to reduce breast cancer risk.

Timing of Environmental Exposures

The biological sequence of events leading to cancer no doubt coincides with certain times of vulnerability during life. Much epidemiological and experiments evidence suggests the need to investigate mutagenic or estrogenic chemical exposures that occur early in a woman's life, even in utero.[229] Studies of breast cancer suggest that the intrauterine environment, age at menarche, and age at first birth, as well as the interval between these latter two events may be critical periods in the development of breast cancer.[230, 231] This may be because the breast cells are undergoing differentiation and proliferation during this interval and therefore are more vulnerable to carcinogenic exposure.[232] Experimental research has established that tumor initiation is most effective during early breast development.[233-236] Furthermore, laboratory studies have found that chemical prenatal exposures can alter ductal and lobular development within the breast.[237]

In animals, a large number of chemical exposures may alter the onset of puberty (vaginal opening).[238, 239] It has been noted that among girls exposed to higher versus lower levels of PCBs in utero experience an earlier age at menarche.[240] As mentioned above, earlier age at menopause has been associated with smoking.[241] In addition, Rogan and colleagues observed a shortened duration of lactation among women with the highest exposures to DDE.[242, 243] These findings emphasize the need to pursue more research to identify environmental exposure experiences in early life that may affect breast cancer risk.

Environmental Exposures that Interact to Influence Breast Cancer Development

The majority of environmental exposures discussed above either exist at concentrations too low or have carcinogenic potential too weak to be easily identified as risks factors for breast cancer, other than ionizing radiation. Therefore modifying factors that make some women susceptible to the effects of environmental carcinogens and/or their combinations must be elucidated to identify the role that they play in the development of breast cancer. Exposure assessments and factors that create or influence susceptibility to breast cancer can be divided into two broad contexts; environment and environment interactions, and environment and gene interactions.

Environment and Environment Interactions

Mammary gland 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 risk factor assessments.

Many in vitro studies have found the effects of environmental carcinogens to be additive.[244-245] Environmental factor interaction may also occur between exposures of very different origins, such as chemicals and viruses. Solvents, DDT, dioxin, and PCBs are immunotoxic,[247] and some chemicals of this kind have been implicated as cofactors in hematopoetic malignancies that may have a vital etiology, such as B-cell lymphomas. In addition, by compromising T-cell immune function, some OCs may serve as late stage promoters of cells that originate through other mechanisms. 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.[248] BMI has been reported to be associated with higher levels of circulating OCs in women.[249-251] In addition, alcohol intake has been associated with higher estrogen and androgen levels in women, especially among pre-menopausal women.[187] 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.

It is also important to examine the association between cancer protective factors and environmental risk factors for breast cancer. As mentioned above, vitamin D and calcium are thought to play an important role in reducing breast cancer risk. A stronger protective effect has also been noted for the consumption of higher versus lower intake of fruits and vegetables among: (1) pre- and post-menopausal women, (2) women who consume more alcohol compared with those who consume less, and (3) women with a family history of breast cancer compared with those without.[252, 253] In addition, a few hours of vigorous physical activity per week has been associated with an approximately 30% reduction in breast cancer risk.[254]

Environment and Gene Interactions

Because high-risk mutations in *BRCA*1 and *BRCA*2, and a few other rare gene variants (*ATM*, *P*53, *PTEN*) account for only 5% of all breast cancers,[255] a substantial component (roughly a fifth) of breast cancer risk may be determined by the combined effect of many low-risk gene variants. Classes of metabolizing genes that are thought to modify breast cancer risk by altering the metabolism of environmental carcinogens are listed in **Table 4**.[256] These genes

Table 4. Metabolizing Genes that Modify Breast Cancer Risk

Phase I: Activation
- *CYP*
- *NAT*
- *COMT*
- *Epoxide hydrolase*
- *Peroxidase*
- *Lypoxygenase*

Phase II: Conjugation & Detoxification
- *NAT*
- *COMT*
- *GST*
- *SULT*
- *UDP-Gluconyltransferase*

CYP = cytochrome P450, NAT = *N-acetyl transferase, GST= glutathione-S-transferase, COMT* = catechol-O-methyltransferase, *SULT* = sulfotransferase.

control the Phase I enzymes that are responsible for converting environmental carcinogens to mutagenic metabolites, and the Phase II enzymes that convert mutagenic metabolites of environmental carcinogens to inactive forms. If detoxification of these mutagenic metabolites fails to occur, genetic mutations may result due to lack of DNA repair. Besides the involvement of the *BRCA* genes in DNA repair, the base excision repair gene, *XRCC1*, has been found to be associated with increased breast cancer risk. *P*53 is best known as a tumor suppressor gene, but also has DNA repair functions.[257] **Figure 8** provides a schematic for DNA damage by a mutagenic metabolite that results in a *P*53 gene mutation.

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 carcinogensisis (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.[255] *P*53 is overexpressed in approximately 40% of breast tumors, with approximately 20% having mutations in the gene. Environmental carcinogens, such as the PAHs and ionizing radiation, have been linked to specific mutations along the *P*53 gene in breast cancer. Furthermore, *P*53 overexpression in breast cancer tumors is associated with a history of smoking, which is consistent with the genotoxic effect of smoking.[258, 259]

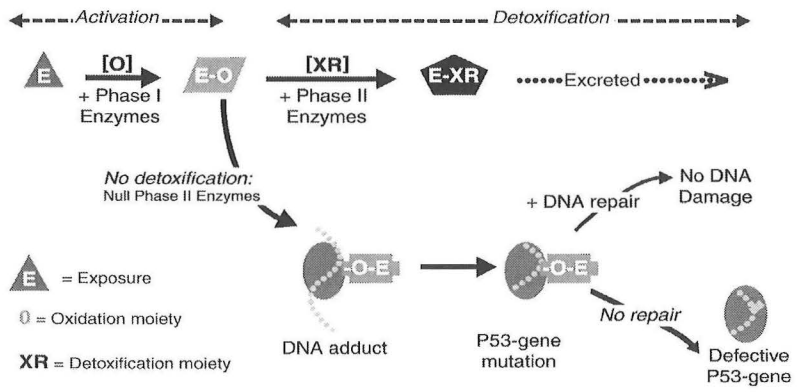


Figure 8. Schematic for the development of a *P*53 gene mutation by an enzymatically oxidized environmental toxin (E-O) due to null phase II metabolizing enzymes. *Adapted from Wolff MS, Britton JA, Wilson VP. Environmental risk factors for breast cancer among African-American women. Cancer 2003;97(Suppl1):289-310.*[260]

Conclusions

Overall, experimental and epidemiological research suggests that environmental exposures and genetic predisposition 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.

Recommendations

In general, research designed to address innovative and emerging hypotheses may potentially advance the knowledge of environmental factors in 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. The following ideas for further epidemiological research related to the effect of environmental factors on the development of breast cancer have emerged based on the content of this report.

New Environmental Exposures

- Environmental and industrial chemicals
  - persistent or prevalent endocrine disruptors
  - compounds to which occupational groups with high breast cancer risk are exposed
  - compounds that have induced mammary gland tumors in laboratory animals, especially those that are prevalent in the environment
- Pharmaceuticals, including SSRIs and tricyclic antidepressants
- Viruses, especially the EBV and MMTV

New Methodological Approaches

- Combine the results of surveillance data, animal research and analogies made with other diseases and risk factors to generate new hypotheses
- Consider the timing of the exposure
  - determining exposures over a lifetime, relative to developmental events
  - developing innovative methods for determining exposure during early life stages
- Use biomarkers of exposure to measure internal dose more precisely
- Validate methods for exposure assessment
- Investigate interactions (including cancer protective factors)
  - gene-environment
  - environment-environment
  - environment-hormone interactions

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