Breast Cancer: Peer-Reviewed Analysis

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Breast Cancer and the Environment

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The Disease

Breast cancer is a very common disease and an increasing concern for women in the U.S. and in many other industrialized countries. One out of every three newly-diagnosed cancers in women is a cancer of the breast, and if current incidence rates hold steady, one out of every eight women in the United States will develop breast cancer during her lifetime (Kelsey and Bernstein 1996). Breast cancer is second only to lung cancer as a cause of cancer-related deaths in women. About one in every four women with breast cancer will die of the disease. Although 99% of breast cancer cases occur in women, this cancer can also affect men, and the outcomes in men are more likely to be fatal (de los Santos and Buchholz 2000).

Breast Cancer Epidemiology: Prevalence and Trends

The incidence rate (reflecting the annual number of new cases) has been rising for fifty years, with a particularly steep rise during the 1980's, and some flattening during the 1990's (Kelsey and Bernstein 1996). Overall, the rate has been increasing by an average of 1-2% per year. Although some scientists contend that the increase reflects early detection due to mammography, many researchers believe that the increase is real, since earlier detection of cancers would not be expected to cause long-term, steady increases in the number of cases, including the observed increasing rates of breast cancer in young women.

Breast cancer is a disease of industrialized, westernized countries. Historically, rates have been highest in the United States and Western Europe, and low in Africa and Asia. However, in recent years, incidence rates have risen steeply in some traditionally low risk countries such as Japan and several Eastern European countries. When individuals emigrate from a country with low rates of breast cancer to an area with high rates, their risk of breast cancer rises. By the second generation, the children of immigrants have a risk of breast cancer equal to the rest of the U.S. population (Kelsey and Horn-Ross 1993).

In the U.S., black women have lower rates of breast cancer than white women, although the rates are paradoxically higher among black women in premenopausal age goups. Breast cancer takes a much more severe course in black women. The rates of metastatic breast cancer are about twice as high in black women, and five-year survival rates are around 60% as compared to about 80% in white women. There are two main theories as to why these differences exist. The poorer outcomes among African-American women may be due to decreased access to health care, resulting in diagnosis later in the course of the disease. This theory is somewhat weakened by the fact that African-American women also have poorer survival than white women at the same disease stage. Others point out that there are subtle by important differences in the cancers that occur in white women and black women, and the latter are more likely to get tuors that are difficult to treat. (Chen et al. 1994) For example, black women are more likely to get cancers that are estrogen receptor-negative (Gordon 1995). These cancers tend to be harder to treat and more aggressive. Unfortunately, few studies have focused specifically on causes of breast cancer in African-American women, so there is little information available to help understand the reasons for the poorer outcomes in this population. The situation becomes even more confusing because male breast cancers are more common among black men than among white men (Meguerditchian et al. 2002).

The Causes of Breast Cancer: What Is Known?

There are few known causes of breast cancer, although there are numerous factors that have been identified as associated with a higher risk of developing the disease (Sasco 2001). One of the known causes of breast cancer is ionizing radiation, an environmental factor. There is also intense research into other possible environmental risk factors for breast cancer, including pesticide exposures, secondhand smoke, air pollutants, and estrogenic chemicals in the environment. Despite some excellent epidemiologic research, the scientific studies looking at breast cancer and environmental toxicants are extraordinarily conflicting, with a frustrating lack of clear, cohesive answers.

The particularly conflicting nature of the breast cancer studies may have several explanations. Breast cancer is a multifactorial disease, meaning that many different genetic, lifestyle, and environmental factors contribute to the development of an individual case of cancer. This makes it difficult to pin down any one exposure amid the multiplicity of possible factors, and link it specifically to the disease. Genetic and environmental factors may also interact, so that some women may be more susceptible to environmental toxicants. If researchers do not know how to separate out the more susceptible women from the less susceptible, studies may appear to find conflicting results. Breast cancer also has a very long latency period -- probably several decades elapse between the causal factors and the eventual appearance of disease. Some researchers believe that changes occur to the developing breast tissue during the prenatal period or in childhood that may predispose to breast cancer decades later (Trichopoulos 1990). It is very difficult to evaluate what a woman was exposed to early in life when most studies first interview women or evaluate exposures in adulthood.

Although genetics have received a lot of attention in breast cancer research, mutations in the known genes that confer increased susceptibility to breast cancer, BRCA1 and BRCA2, are estimated to be present in less than 10% of cases of the disease (Nicoletto et al. 2001). A study of twins that compared cancer risks of identical twins and fraternal twins estimated the proportion of cancer that is due to inherited genetic factors vs. environmental factors. In this study, an estimated 27% of breast cancer could be explained by inherited genetic factors. The range of estimates of possible genetic risks for breast cancer in this study was fairly broad, spanning 4-41% (Lichtenstein et al. 2000). That leaves a large proportion of breast cancer—probably two-thirds or more of cases— unexplained by inherited genetic factors.

Factors known to be associated with higher risk of developing breast cancer include early age menarch (the first onset of menstrual cycle), late age at menopause, shorter menstrual cycles, late age at first full-term pregnancy, fewer children, not breastfeeding, and obesity after menopause (Key et al. 2001). These risk factors are unified by most researchers into the theory that longer and higher-level exposures to the hormone estrogen, and perhaps also to progesterone, are associated with increased risk of breast cancer (Davis et al. 1997). This theory makes sense because many types of breast cancer cells are known to proliferate in response to estrogen. Menstrual cycling causes women to go through the so-called luteal phase (premenstrual phase) every month when the levels of both estrogen and progesterone in their bodies are quite high. Each monthly cycle therefore exposes the breast to a burst of hormones that can promote the growth of a cancer. The risk factor of obesity after menopause also fits into the estrogen hypothesis. Fat cells convert androgens from the adrenal gland into estrogens. Hormone replacement therapy has also been shown to increase risk of breast cancer by 25-50% after five years of treatment, as would be expected from the associations between estrogen and progesterone and breast cancer (Writing Group 2002).

Exposure before birth to the artificial estrogen diethylstilbesterol (DES), a drug widely used in the 1950's and 1960's, has been shown to increase breast cancer risk by 2.5-fold, indicating that prenatal exposures to estrogens may predispose to breast cancer many decades later (Palmer et al. 2002). The prenatal estrogen exposure hypothesis is supported by various other observations, including that twins and women with higher birthweights are at higher risk of breast cancer. Twin pregnancies and higher birthweight babies are both associated with higher estrogen levels in pregnant women (Potischman and Troisi 1999). In addition to the estrogenic effects discussed above, pregnancy and breastfeeding cause the breast to fully mature. Until pregnancy, the cells in the milk ducts, and milk producing structures of the breast remain immature. Immature cells are more susceptible to cancerous changes compared to fully developed cells. The estrogen hypothesis is further supported by the fact that higher levels of estrogen have also been associated with breast cancer in men (Meguerditchian et al. 2002).

Some researchers have reported that girls are showing signs of puberty at an earlier age today than they did in the past (Herman-Giddens et al. 1997). If menstrual cycling begins at an earlier age, then breast cancer risk is likely to rise since early menarche is a known risk factor for breast

cancer. It is not yet clear why the age at puberty may be declining in girls. Researchers have proposed a variety of hypotheses ranging from dietary factors, to exposures to estrogenic chemicals in cosmetic products and the environment.

Diet

The much higher rates of breast cancer in westernized countries has led to some scrutiny of the dietary patterns in different regions. Immigrants to the U.S. and other western countries often change their dietary habits dramatically in the course of a generation. This change could contribute to the dramatic increases in breast cancer risk seen when people emigrate from low risk countries to the U.S. The traditional diet in many Asian and African countries is low in fat and includes primarily complex carbohydrates. When compared to women eating traditional diets, women consuming a western diet have different hormone profiles. Women eating a high fat, high protein diet with mostly refined carbohydrates and sugars have higher levels of sex hormones in their blood, lower excretion of extrogens in their feces, and lower levels of a protein called sex hormone binding globulin (SHBG) Adlercreutz 1990). This protein attaches to estrogen, making the estrogen temporarily inactive. High fiber diets have been shown to increase elimination of estrogen and its metabolites in the feces, thereby lowering circulating estrogen levels (Adlercreutz 1990).

The traditional Asian diet also contains large amounts of natural estrogens, known as phytoestrogens. These weak estrogens, found naturally in soy, nuts, and whole grains, have received some attention in the breast cancer community (Bradlow and Sepkovic 2002). In adult or adolescent women, phytoestrogens may modulate the effects of endogenous estrogens. Phytoestrogens also may increase the levels of SHBG and may act on the hypothalamus and pituitary gland, causing them to send the ovaries a signal to reduce production of estrogens (Adlercreutz 2002). However, studies in animals and humans have failed to find evidence that phytoestrogens protect against breast cancer (Adlercreutz 2002). In the fetus, the effects of phytoestrogens may be more clearly adverse. In rodent studies, short-term exposures to phytoestrogens during critical periods of fetal development can cause cancer (Newbold et al. 2001).

Environmental Exposures

Ionizing radiation, alcohol, and synthetic estrogens are known causes of breast cancer. Many other environmental exposures are being studied as possible breast carcinogens, but the data so far are conflicting and uncertain. Electromagnetic fields and light at night have shown associations with breast cancer in a few studies. Much research has focused on several pesticides, including DDT and dieldrin, and on the polychlorinated biphenyls (PCBs). The data linking these chemicals to breast cancer in humans is conflicting. Because estrogens are known to promote the development of breast cancers, the finding that numerous pesticides, and chemicals in plastics, cosmetics, and foods can mimic estrogen provides particular reason for concern. Although endocrine disrupting chemicals are an important research question, with the exception

of estrogenic drugs such as diethylstilbesterol (DES), hormone replacement therapy, and possibly the pesticide dieldrin, the links to breast cancer remain mostly hypothetical in humans. Numerous common environmental chemicals have been found to cause mammary gland tumors in laboratory rats or mice. Only a few of these chemicals have been studied in humans, and this is a fertile area for future research. The polycyclic aromatic hydrocarbons (PAHs), chemicals found in soot and smoke, are known carcinogens that have been linked to mammary tumors in animals. Several studies have found associations between exposure to PAHs and breast cancer in humans. All of these issues are discussed in greater detail below.

Ionizing Radiation, Electromagnetic Fields, and Light at Night: Ionizing radiation (the type found in X-rays, atomic bomb explosions, and other nuclear materials) is an established cause of breast cancer in humans. Survivors of the atomic bomb explosions in Japan have an increased risk of breast cancer, and women who have undergone medical treatments involving extensive radiation to the chest also have an increased risk (John and Kelsey 1993). The research on radiation has clearly established the importance of the timing of environmental exposures to a carcinogen. Radiation exposure after about age 40 has little detectable effect on breast cancer risk, whereas before age 20, the effect is highly significant, and up to a nine-fold increased risk has been reported in some studies (Tokunaga et al. 1987). This increased risk first becomes evident about 10-15 years after the exposure and persists throughout the individual's lifetime (John and Kelsey 1993). It appears that the breast is most sensitive to radiation before the first pregnancy—a finding consistent with the theory that the final development of the milk ducts that occurs during pregnancy and lactation increases the resistance of the cells to cancer.

An electromagnetic field (EMF) is a form of non-ionizing radiation emitted by electric power generation, power lines, and some appliances. Because this type of radiation does not penetrate deep into the body, it was initially thought harmless. More recently, it has become controversial due to research linking EMF exposure with childhood leukemia. Some researchers have theorized that EMF acts like visible light by affecting the body's daily fluctuations in the hormone melatonin. Melatonin is normally secreted by the pineal gland in the brain during the night. This hormone appears to modulate levels of estrogen and also appears to have anti-cancer effects. Some studies have reported up to a six-fold increased risk of male breast cancer in electricians, telephone linemen, and electric power workers, whereas other large, well-designed studies have failed to find any such association (Ahlbom et al. 2001). Because male breast cancer is such a rare disease, few studies have the statistical power to detect or confirm a small increased risk if such a risk exists. Studies looking at female breast cancer and occupational exposure to EMF are limited because of the lack of women in highly exposed populations. Investigations of household EMF and breast cancer risk have mostly been negative, but some have shown slightly elevated risks among younger women (Ahlbom et al. 2001). Several major studies on EMF and breast cancer are ongoing and should help to clarify this issue.

Because melatonin release occurs during the nighttime hours and is inhibited by light, research has begun to focus on women who are exposed to light at night (Poole 2002). Studies of nurses

have found associations between a history of shift work and breast cancer (Schernhammer et al. 2001). The risk of breast cancer was reported to increase slightly but significantly with increasing frequency and duration of work in the middle of the night during the ten years prior to diagnosis. Regular work on the graveyard shift was associated with a 60% higher risk of breast cancer (Davis et al. 2001). Studies asking about light in the bedroom were less impressive, with only a slight increase in possible risk among those women with the brightest bedrooms (Schernhammer et al. 2001).

Organochlorine Pesticides, PCBs, and Dioxins: Dozens of studies have looked for possible links between breast cancer and exposure to pesticides such as DDT and dieldrin, as well as for links with polychlorinated biphenyls (PCBs) and dioxins. DDT and dieldrin are pesticides that were banned in the late 1970's in the U.S. and in many other countries. These chemicals accumulate in fatty tissues such as the breast, where they persist for decades. PCBs also accumulate in fat and are persistent. These chemicals were used as electrical insulators, fire retardants, and industrial lubricants for many years, but were banned around the same time as DDT. Dioxins, such as 2,3,7,8-tetrachlorodibenzodioxin, are byproducts of many industrial processes and incineration.

DDT, dieldrin, and some PCBs have been shown to mimic estrogen and can promote the growth of mammary tumor cells in laboratory dishes and in rats (Shekhar et al. 1997). Interestingly, the metabolic byproduct of DDT, known as DDE, is not estrogenic but rather is an anti-androgen (it blocks male hormones such as testosterone). Several small studies in the 1980's reported higher levels of DDE in the breast fat of women with cancer. These findings spurred extensive research into links between breast cancer and residues of organochlorines in blood and breast fat. Most of the more recent and larger studies have found no association between levels of DDE or PCBs and breast cancer (Laden et al. 2001; Gammon et al. 2002). However, the literature thus reveals a perplexing patchwork of positive and negative studies without a clear explanation for the marked discrepancies in the results (Snedeker 2001). Researchers have proposed many possible reasons for the discordant findings. Some of the theories center around differences in the analytic methods used in the studies, whether women were exposed originally to estrogenic DDT itself from direct spraying, or only to DDE from food residues, or whether DDE is acting as a marker for a different, unknown, chemical that may be associated with breast cancer.

One California study indicated that racial differences may be important with regard to DDT. In this study, no association was found between DDE and breast cancer in white women, and an inverse association was seen in Asian women. Black women, in marked contrast, had higher levels of DDE in their bodies compared to the white women, and there was an association between DDE levels and breast cancer (Krieger et al. 1994). The racial differences persisted even when the researchers took into account a long list of factors including age, socioeconomic status, pregnancy history, place of birth, and others. Many studies have consistently found that black women have higher levels of DDE in their bodies compared with white women, but no other

studies have been done to confirm the association between DDE and breast cancer in black women.

It is possible that some women are more genetically susceptible to organochlorine chemicals and may therefore be at risk of breast cancer after exposure, whereas others are not susceptible (Wolff and Weston 1997). Such a difference could explain the discordant results reported in various studies, but such susceptibility factors, if they exist, have not yet been identified. In addition, the timing of exposure may be critical with these chemicals just as it is with radiation. Studies measuring levels of organochlorines in middle-aged women probably do not accurately estimate the exposures to these women during childhood. One study avoided this problem by looking at stored blood samples taken between 1959 and 1967 from 262 women in California, about half of whom had developed breast cancer. At the time of the sampling, the average age of these women was 26 years. The study demonstrated a strong, statistically significant association between breast cancer and higher levels of DDT, but only among women who were exposed to DDT before age 15 years. In addition, the researchers found a negative association between breast cancer and levels of DDE, demonstrating both the importance of the timing of exposure and the major differences between DDT and DDE (Cohn et al. 2002).

The pesticide dieldrin, an unmeasured confounder in some of the PCB and DDE studies, might be the missing breast cancer link. Two Danish studies found significant associations between dieldrin and breast cancer risk, including more aggressive disease and poorer survival in women with higher dieldrin levels (Høyer et al. 1998; Høyer et al. 2000). These studies were well-designed and the results appeared to be robust. However, a large study of breast cancer on Long Island, NY failed to find any associations between dieldrin levels in blood and breast cancer risk (Gammon et al. 2002b). The overall situation regarding organochlorines and breast cancer risk is confusing. The results on DDE in black women, DDT exposure in early life, and the Danish studies on dieldrin clearly all need further investigation.

Dioxin is known to cause cancer in numerous different organs in both humans and animals. However, dioxin is also anti-estrogenic, causing some researchers to theorize that it is less likely to promote breast cancer. These opposing properties of dioxin may explain why some studies found an association between exposure to this chemical and breast cancer, whereas other studies found no association between exposure and risk. An initial study of women exposed to dioxins from an industrial accident in Seveso, Italy initially found no increased risk of breast cancer, but more recent follow-up studies of this cohort of women that included measured levels of dioxin body burdens reported a doubling in breast cancer risk starting to appear twenty years after the accident (Warner et al. 2002). Important research in the laboratory indicates that the timing of dioxin exposure may be critically important. Rats exposed to small amounts of dioxin prenatally and in infancy had altered development of the mammary glands in a manner that would tend to predispose to cancer development (Fenton et al. 2002). Over time, these abnormalities persisted and the rats were more likely to develop tumors as they aged (Brown et al. 1998).

Soot and Secondhand Smoke: Chemicals found in soot and smoke are known to cause mammary gland tumors in laboratory animals. These chemicals are known as polycyclic aromatic hydrocarbons (PAHs) and aromatic amines. Most people are exposed to PAHs from cigarette smoke, diesel exhaust, air pollution, and to both PAHs and aromatic amines from residues on smoked, grilled or charbroiled meats. PAHs are powerful mutagens (they attach to DNA and cause damage to chromosomes), accumulate in breast tissue, and are used experimentally to induce mammary tumors in lab rats for research purposes. Several studies have found links between PAHs and breast cancer. Various studies have reported increased breast cancer risk of between 50% and five-fold with exposures to PAHs (Rundle et al. 2000; Gammon et al. 2002a). The research is confusing because the studies have found associations between measured levels of PAH-DNA adducts in these women and breast cancer risk, but failed to find significant associations between reported consumption of grilled or charbroiled meat and breast cancer, or between air pollution exposure and breast cancer. The PAH-DNA adducts are biological markers of genetic damage from PAHs. The researchers theorize that some women may be less able to deactivate and eliminate PAHs and may therefore have more of the dangerous adducts, whereas others exposed to PAHs may form fewer adducts and be less susceptible to cancer from these chemicals.

Studies specifically on exposure to cigarette smoke show an interesting paradox. Smokers are not usually reported to have an elevated risk of breast cancer, whereas secondhand smoke does appear to slightly increase the risk of breast cancer (O'Connell et al. 1987; Khuder and Simon 2000). There are several possible explanations for this counter-intuitive finding (Morris and Seifter 1992). Sidestream cigarette smoke contains up to ten times the concentration of toxic PAHs and benzene compared to the smoke drawn through the filter. Smoking also appears to be anti-estrogenic, since smokers often have early menopause and lower estrogen levels. Some toxins in cigarette smoke, such as cyanide, can also inactivate the cytochrome p450 enzymes that are responsible for activating PAHs into more dangerous forms. These factors could help explain why the breast cancer risk from second hand smoke equals or exceeds the risks from direct smoking. Numerous chemicals that are present in cigarette smoke cause mammary cancers in laboratory animals. One review reported eleven constituents of cigarette smoke that are known mammary gland carcinogens in animals. These chemicals include benzo[a]pyrene, dibenzo[a,l]pyrene, 2-toluidine, 4-aminobiphenyl, 2-amino-3-methylimidazoquinoline, 2-amino-1-methyl-6-phenylimidazopyridine, butadiene, isoprene, nitromethane, ethylene oxide, and benzene (Hecht 2002).

Genetic susceptibility may be at work in smokers also. A set of enzymes known as the N-acetyl transferase (NAT) enzymes, are partially responsible for the detoxification of hazardous agents such as the PAHs. Women with a particular genetic variant in the NAT enzyme system ("slow acetylators") have a 70% increased risk of breast cancer if they smoke. In contrast, the opposite genetic variant, or "fast acetylators" have a doubling of breast cancer risk from exposure to second hand smoke (Chang-Claude et al. 2002). The timing of exposure may also be particularly

important in the case of PAHs and other components of cigarette smoke. PAHs act somewhat like radiation in that they cause genetic mutations that may initiate cancerous changes in breast cells. It is likely that exposures early in life may be the most significant in predisposing to breast cancer development. The studies finding positive associations between cigarette smoking and breast cancer, in fact, were those that looked specifically at women who smoked during their teenage years (Wolff et al. 1997). Therefore it is possible that exposures to smoke, air pollution, diesel exhaust, and dietary PAHs in smoked, grilled, and charbroiled meats may be of particular concern in young girls and teens.

Alcohol and Solvents: Organic solvents include alcohols; aromatic solvents such as benzene and toluene found in gasoline, glues, or paints; and chlorinated solvents such as the perchloroethylene used in dry cleaning, or trichloroethylene, which is a common drinking water contaminant. These chemicals are volatile so they are easily inhaled, and they are absorbed through the skin. They are attracted to fat, but do not persist for very long in the body. Measured levels of solvents in the blood, urine, or exhaled breath only reflect exposures during the past few hours or days. Because of their short-lived nature, it has been difficult to study links between solvent exposure and breast cancer.

Ethanol, the substance in alcoholic beverages, is considered to be a known breast carcinogen (Singletary and Gapstur 2001). Consumption of two or more glasses of wine per day has been shown to increase the risk of breast cancer by about 50% (Horn-Ross et al. 2002). Alcohol may increase breast cancer risk by increasing estrogen and androgen levels, or by various other mechanisms (Davis et al. 1997). In addition, alcoholism is often associated with dietary deficiencies that can increase susceptibility to carcinogens.

Several solvents are known to cause tumors of the mammary gland in laboratory rodents. These include benzene, 1,2-dibromoethane, 1,2-dichloroethane, methylene chloride, styrene, 1,2,3-trichloropropane, and vinyl chloride (Dunnick et al. 1995). A few occupational studies have reported increased breast cancer risk among women in solvent-exposed industries, although most workplace studies did not report an increased risk (Labreche and Goldberg 1997). The worker studies were not designed to study breast cancer, and most contained very few women and used broad occupational groupings as a proxy for exposure. Therefore the data on organic solvents and breast cancer require additional attention and further research.

Summary

In summary, breast cancer is a complex, multifactorial disease that is caused by the interaction of genetic and environmental factors. Because the disease is so common, and is on the rise, it is important to identify any contributing environmental factors so that we can decrease exposures and prevent disease. It is clear that some environmental factors, such as exposure to radiation and synthetic estrogens, can cause breast cancer. The extensive research into other possible causes has been confusing and conflicting, but has revealed numerous possible contributing factors. The confusing nature of the existing data calls for further research to attempt to sort out some of the

key unanswered questions, and also calls for precautionary actions to prevent unnecessary exposures to avoidable factors that may be associated with breast cancer.

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