Rethinking Breast Cancer Risk and the Environment: The Case for the Precautionary Principle

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The World Health Organization recently reported that breast cancer has become the most common cancer in women throughout the world. Known risk factors account for less than half of all cases of breast cancer, and inherited germ line mutations occur in at most only 10% of all cases. Cumulative exposure to estradiol and other hormones links many of the established risk factors for breast cancer. This paper reviews epidemiologic and toxicologic evidence on breast cancer risks and presents a comprehensive construct of risk factors intended to focus on the identification of those factors that can be controlled or modified. We attempt to provide a framework for interpreting the etiologic interplay of endogenous metabolic changes and environmental changes in the etiology of breast cancer. The construct we develop distinguishes between those risk factors that are directly causal, such as ionizing radiation and inherited germ cell defects, those vulnerability factors that extend the time period during which the breast undergoes development, and those contributing factors that increase total hormonal stimulation of the breast. Some hormonally active compounds, such as those in soy and broccoli and other phytoestrogen-containing foods, can be protective against breast cancer, while others, such as some environmental contaminants, appear to increase the risk of the disease by increasing levels of harmful hormones. Efforts to explain patterns of breast cancer should distinguish between these different risk factors. Identification of vulnerability and contributing risk factors can foster the development of public policy to reduce the burden of this prevalent cancer. Prudent precautionary principles suggest that reducing exposure to avoidable or modifiable risk factors should receive high priority from the public and private sectors.

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The Precautionary Principle

We must act on facts, and on the most accurate interpretation of them, using the best scientific information. That does not mean we must sit back until we have 100% evidence about everything. Where the state of the health of the people is at stake, the risks can be so high and the costs of corrective action so great, that prevention is better than cure. We must analyze the possible benefits and costs of action and inaction. Where there are significant risks of damage to the public health, we should be prepared to take action to diminish those risks even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it.

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The World Health Organization recently reported that breast cancer has become the most common cancer in women throughout the world (1–3). The causes of this global pattern are not well understood. In those few countries where mammographic screening is routinely available, such as the United States and some provinces of Canada, increased ascertainment accounts for some of the recorded increase in incidence. In the United States recently, declines in breast cancer mortality have been reported for white and African-American women under 65 years of age (4). But changes in known risk factors, diagnostic procedures, or aging cannot account for domestic and worldwide patterns in breast cancer incidence and mortality. From 1973 to 1987, when routine population mammographic screening was not yet practiced, age-adjusted mortality increased in both developed and developing countries (see Fig. 1 and 2). During this period, breast cancer mortality grew 20% or more in several central European countries and Japan, with rates of breast cancer being about four times lower in most Asian countries.

Established Risk Factors for Breast Cancer

Less than 10% of all breast cancer develops in women who have inherited germ cell mutations such as loss of tumor-suppressor genes including p53, BRCA1, BRCA2, or ATM (5,6). Established risk factors, which have been identified in less than half of all women with breast cancer (7), include inherited genetic defects, menarche before age 12, menopause after age 55, having either no pregnancy or late childbearing, no lactation, early or repeated exposures to radiation, prolonged use of hormone replacement therapy, increased breast density, higher socioeconomic status, and postmenopausal obesity. Most of these risk factors can be linked with increased lifetime exposure to estrogen, other hormones, and higher exposures early in life (8–11). Most of these risk factors are not easily modifiable (12). Breast development depends on the complex interplay of estrogen, progesterone, and other growth factors. Therefore, the earlier in life that regular menses begins and the later that it ceases, the greater exposure to hormones that affect breast growth in a woman's life (13).

Risk Factors

In an effort to identify public policies that can be developed to reduce breast cancer, this paper distinguishes between risk factors that directly cause breast cancer, those that delay the time period of vulnerability of the breast by prolonging breast development and consequent susceptibility to damage, and those that contribute to altered levels of cancer-causing endogenous or xenohormones. What exactly do these demonstrated risk factors for breast cancer tell us? In fact, with the notable exceptions of ionizing radiation and inherited genetic damage, none of the established risk factors for breast cancer directly causes the...
disease (14). Radiation and inherited defects can be said to cause breast cancer in that they produce alterations in cell growth, repair, and metabolism that are understood to be mechanistically linked to the development of breast cancer. According to accepted epidemiological criteria, risk factors can be extracted from studies that consistently reveal an association between certain conditions that precede the development of breast cancer (15). Even where such criteria are met, a fundamental question must be answered: Is the association between these risk factors and the disease due to a direct mechanism or causal link? Outside of pharmaceutical and other medical interventions such as diagnostic radiation, which are studied under controlled conditions, few human exposures can be directly linked with specific health consequences.

A variety of studies indicate that the potential for aberrant growth is dependent on two factors: the rate of cell growth and the extent of exposure (16). Even for ionizing radiation, the same dose can produce differential responses depending upon the timing of exposure. Studies have consistently confirmed that females exposed to radiation prior to puberty have a much greater risk of developing breast cancer than do older women subject to the same levels of exposure (9).

These findings about radiation and breast cancer highlight a profoundly important component of risk factors for diseases with long latency: timing of exposure can be more important than dose. Radiation during the critical periods when breast cells are first forming prenatally or during early adolescence induces proportionally more neoplastic transformation of cells and is thereby more carcinogenic than exposures that occur later in life (17). This suggests that other carcinogenic exposures which occur when breasts are undergoing rapid cell differentiation, cell growth, or development of the whole gland during puberty could also be especially important causes of breast cancer.

**Vulnerability Factors**

More rapidly developing cells, such as those of the prepubescent breast, are at a special state of vulnerability. Vulnerability factors for breast cancer are those that extend the time during which the breast is growing and the rate of this growth. For instance, early menarche, no lactation, and late menopause prolong the time period during which the developing breast is potentially exposed to estradiol and deleterious agents (see Fig. 3). Evidence for this increased vulnerability is provided by observations of women born to mothers who had unusually high or low levels of estrogen during pregnancy. Toxemia is tied with preeclampsia and lower levels of estrogen. Women born to mothers who were toxemic had an adjusted odds ratio (OR) of 0.41 for breast cancer compared to those who underwent normal pregnancy. In contrast, women who experienced elevated levels of hormones prenatally or neonatally were found to have an OR of 3.96 (18).

Regarding the risk factor of lactation, the situation is complex. Lactation is a potentially modifiable factor that can be considered as both a vulnerability and a contributing risk. Premenopausal women who lactated have a reduced risk of breast cancer, with further significant reductions of risk for women who lactate earlier or for longer cumulative duration. Animal studies have demonstrated that early reproductive life breast tissue is positively influenced by lactation (19). Immediately before and after the termination of pregnancy, the rapidly growing or lactating breast may also be at risk from proliferative processes and agents. After lactation ends, the breast becomes more differentiated, reducing susceptibility to such agents (20). However, postmenopausal women who have lactated do not show reduced risk of breast cancer in comparison to women who have not lactated (19). This may reflect the fact that cumulative exposures to other cancer-causing xenohormones overwhelm any earlier protective effects from lactation.

**Contributing Factors**

Contributing factors can directly affect overall exposure to circulating hormones and can interact with vulnerability factors. Some hormones are potent stimulators of cell growth (21), and some hormonal metabolites can bind to DNA and trigger aberrant cell growth (22,23). Alcohol, lack of exercise,
diets low in fiber and vitamin D, and exposure to some pesticides, solvents, fuels, and pharmaceuticals increase the total amount of bioavailable estradiol (20). Bioavailable estradiol represents the fraction of estradiol that is not readily excreted when bound to sex hormone-binding globulin (SHBG) or albumin (24). This binding reduces the availability of estradiol to the cells. Thus, processes that decrease hormone binding increase circulating levels of estradiol. Contributing factors can also alter metabolism of other growth-regulating hormones that alter breast cell growth and metabolism and increase the likelihood of aberrant cell growth.

Alcohol is a prime example of a risk factor that may increase the circulation of hormones, thereby rendering it a contributing risk factor. A large nurses’ health study (25), later corroborated by a women’s health study (26), determined that postmenopausal women who consumed alcohol manifested a 40% increased risk of breast cancer with estrogen administration, while those who did not consume alcohol or consumed it at levels below the average daily intake of 5 g showed no increased risk. When alcohol interacts with estrogen, the bioavailable estradiol level rises sharply above breast cancer-promoting levels for women in general (27). Another explanation as to why regular consumption of alcohol increases breast cancer likelihood is because ethanol is directly estrogenic (28). When additional direct risk factors, such as inherited genetic mutations and p53 genes (29) are taken into account, the effects of alcohol are magnified (30).

Critical Windows of Exposure

Under this emerging paradigm, three distinct critical windows need to be considered: prenatal, prepubescent, and perimenopausal. Prenatal exposure to elevated levels of estradiol or other growth-regulating hormones throughout gestation may imprint breast cells, making them more sensitive to subsequent exposures. When later exposed to stimulating agents, these primed cells may respond more quickly. Thus, early breast cell growth renders tissue subsequently vulnerable to carcinogens or hormonally active compounds. In a similar manner, prepubescent exposures can expedite the process of aberrant breast growth and attendant susceptibility. More rapidly developing cells may be prone to sustaining aberrant growth, as repair mechanisms can be swamped. Extended lifetime menses or obesity after menopause increases cumulative exposures to hormonal metabolites as adipose cells in fat tissue release estrogens. Thus, exposures at these critical times can alter both the magnitude and extent of hormonal stimulation of the breast.

Role of Hormonal Metabolites

Clinical and animal studies indicate that total lifetime exposure to unbound or bioavailable estradiol predicts risk of breast cancer (31,32). Under one theory, exposures that alter hormonal metabolites can affect the risk of breast cancer working through genetic and/or hormonal paths (33). As to hormonal paths to breast cancer, an array of evidence indicates that different by-products of estradiol oxidation have profoundly different biological effects (see Fig. 4) (34). Estrone in humans is hydroxylated to form one or two irreversible and mutually exclusive pathways—16α-hydroxyestrone (16-OHE1) or 2-hydroxyestrone (2-OHE1) (35). The former metabolite appears to bind covalently to the estrogen receptor (ER), while the latter stimulates cell repair and inhibits cancer. Another estradiol metabolite, 4-hydroxyestrone (4-OHE1), also appears highly carcinogenic, although its significance for humans is not clear (22). Two distinct mechanisms can influence the potential for aberrant cell growth: materials can directly bind with hormone receptors altering cell proliferation, or they can modify breast cell proliferation by affecting the intricate balance between key hormonal metabolites that influence parenchymal growth factors in other ways. Some studies have found that exposing human breast cancer cells that are ER positive to lipophilic organochlorine compounds increases 16-OHE1, and suppresses 2-OHE1 (36), as do known mammary carcinogens such as dimethylbenzanthracene.

Concerning genetic paths, xenohormones can cause structural or functional damage to DNA (37). Functional damage can affect processes of cell growth, the ability of tumor-suppressor genes to restrain malignant growth, and the expression of telomerase to overcome cellular senescence. Such damage impedes critical cell repair systems, hinders recognition of aberrant cells, and allows the accumulation of harmful mutations. Structural damage to DNA can occur from genotoxic agents and from free radical or redox cycling of harmful xenoestrogens that
produce reactive oxygen species. This redox cycling yields high rates of radical-induced DNA damage, including 8-hydroxyguanine and adenine adducts, apurinic sites, or loss of ring opening products (e.g., 2,6-diamino-4-hydroxy-5-formamidopyrimidine) (38,39). Women with breast cancer have been reported to have significantly higher rates of such radical-induced damage than do women without the disease (40).

Not all xenohormones disrupt normal endocrine functioning or damage DNA. Many are "good" xenoestrogens that bind strongly with the ER and appear to have protective effects. Several of these are found in plants, e.g., daidzein, genistein, isoflavonoids, as well as in fish oil (41–43). Some of them appear to serve as antioxidants. Certain good xenoestrogens inhibit angiogenesis or protease or kinase activity. In this manner they can reduce the propensity of aberrant breast cells to proliferate, increase DNA repair, or produce other changes in the genetic or hormonal microenvironments that alter malignant progression (44).

Unexplained Patterns of Breast Cancer

Our proposed conceptual framework can partly account for the observed temporal changes in some established risk factors for breast cancer, such as the decline in age at menarche over the last half-century. It is possible that this decline could reflect changes in both vulnerability and contributing factors. In part, increased total caloric intake in the diet has resulted in girls accumulating proportionally more body fat. Fat is a direct source of estrogens earlier in life. Those who are heavier earlier in life will experience menses and their breasts will begin developing at earlier ages. In addition, the extensive use of growth hormones, including diethylstilbestrol and other estrogenic compounds, in domestic animal products and the bioaccumulation of such xenohormones as organochlorine pesticides may also contribute to early menarche and elevate circulating levels of hormones.

Factors may contribute to breast cancer by impairing the function of tumor-suppres-
sor genes such as p53 expression or by impeding the ability of proteins such as tyro-
sine kinase and protein kinase C functions (45) to detoxify and excrete carcinogens. An expanding scientific literature indicates that prostaglandin levels are higher in cancerous tissue than in normal tissue (46). Cancer of the breast forms more prostaglandins than normal breast tissue (47). Up regulation of the cyclooxygenases (Cox-1 and Cox-2) catalyzes the formation of prostaglandins, which in turn have multiple effects that favor carcinogenesis. Contributing factors that inhibit Cox activity reduce the risk of colon, breast, and lung cancer in animals and humans. Prostaglandins such as PGF 2 and PGE 2 are important factors during fetal development, ovulation, and luteinization. Contributing factors can convert procarcinogens to car-
cinogens via Cox-mediated metabolism of arachidonic acid.

Because carcinogens such as benzopyrene induce Cox-2, these may be important for the development of breast cancer as well. Overexpression of Cox-2 inhibits apoptosis and enhances invasiveness of malignant cells. Young women exposed to agents that exacerbate such overexpression are likely to be at increased risk for cancer. Thus, it is logical to expect that those individuals with inherited or environmentally increased levels of carcinogen-activating enzymes such as Cox-2 will have enhanced cancer vulnerability (48), while those with lower levels will have reduced risk (49). In addition, decreased dietary intake of the natural Cox-2 inhibitors such as soy isoflavones, curcumin, and retinoid is a probable vulnerability factor for the development of breast cancer.

The framework we offer can also account for differences in rates of breast cancer in some areas. Lower rates of breast cancer have consistently been found in women living in Asian countries, although rates have increased recently (50). Pollution in this region is not known to be particularly low; in fact levels are considerably elevated in China (51). But diets have traditionally been rich in protective factors such as soy products, fish, and vegetables and low in animal dairy products that can concentrate some contaminants. These protective factors may account for the relatively low rates of breast cancer and other hormonally mediated diseases in Asian women (50).

Inconsistent Results

Recent human studies have focused on assessing the impact of organochlorine compounds and have not addressed the broad array of other suspect xenohor-
mones, many of which leave no biologic markers, such as benzo[α]pyrene, some plastics, and fuels. Nor have protective fac-
tors such as genistein and other isoflavones been widely studied. Organochlorines have been studied largely because these compounds are persistent and can be measured years after exposures have occurred. Studies of these lipophilic compounds have produced inconsistent results. Results of some of the early studies on organochlorine residues tended to be positive, with higher levels of polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE), either in the blood or in adipose tissue, found among women with breast cancer than in controls (52,53). In addition, nested case–control prospective studies in this field have tended to yield positive results, especially those that have looked at ER positive cases (54). Thus, a small case–control study in Canada found that women with elevated levels of DDE had 8.9 times the risk of ER positive disease than did women with relatively lower levels of this metabolite (54). ER positive cases appear to be increasing overall in women over 60 years of age, according to one report from California (55). In some studies, negative results were also described for the total cancer study population (56) or for specific subgroups of breast cancer subjects, such as Asian women (57).

Three recent case–control studies (56,58,59) of organochlorine residues have reported that when first diagnosed, women with breast cancer actually have lower levels of these compounds in their bodies compared with cases that do not have these diseases. These studies could not examine the role of exposures during critical windows earlier in life, but looked only at residues remaining after the disease was expressed. In all of these studies, levels of these contami-
ants measured after the disease has been detected are severalfold lower than those reported three decades earlier, indicating the success of programs to reduce the use of these materials (4). Negative studies should be considered separately in terms of the regions involved and in terms of the compounds measured.

In two of these studies, which were conducted outside the United States (56,59), the authors have indicated that a majority of the cases were stage II or III when sample collection was undertaken. In these circumstances, preclinical disease may have altered lipid metabolism, which could account for the fact that these patients tended to have lower levels of some organochlorine compounds. One of the studies, which was conducted in Germany, the Netherlands, Northern Ireland, Switzerland, and Spain, found significantly higher means of DDE in controls than in cases (59); the OR comparing the highest to the lowest tertiles of DDE indicated a reduced risk for the most highly exposed subjects. Results are less clear in the other study (61), which was conducted in Mexico, a country where DDT is still in use. The arithmetic and geometric means of DDE were somewhat higher among cases than among controls; but this finding was not statistically significant. However, reduced ORs were found when the highest and lowest tertiles were compared (56).
In the United States, a recent nested case–control study of the Nurses' Health Study (58) examined 240 cases, 200 of which involved invasive disease. Samples obtained in the 2 years before diagnosis showed relatively low levels of DDE metabolites in this group, with levels being six times lower than those found in U.S. women in the 1970s (58). As with the recent foreign studies, it is unclear whether these lower levels in cases are a consequence of the disease because blood was analyzed when the cancer process had been underway for periods of up to a decade or more. Also, data were not collected on the role of protective factors such as natural Cox-2 inhibitors and protective phytoestrogens, such as those found in soy and fish oil, nor was information obtained on possible exposures earlier in life. Moreover, residues of DDE measured in the plasma did not show the same estrogenic activity as the parent mixture. In fact, DDE acts primarily as an antiestrogen (60). The most highly estrogenic contaminants cannot be detected years after exposure.

A more recent report from this same research group used a prospective design and confirmed that early exposures to growth factors can be significant, especially for premenopausal causes of breast cancer. This new study found that premenopausal cases of breast cancer with the highest levels of insulin-like growth factor-1 as measured 4 years or more before diagnosis had nearly a sevenfold greater risk of breast cancer compared to those without the disease (61). This finding indicates the importance of looking at a broad array of potential protective and disruptive factors, as well as the value of conducting longer term prospective studies that permit their identification.

Studies that consider current levels of metabolites of pesticides in cancer patients have been described as analogous to "looking under the nearest lamppost for lost keys because that is where there is light" (60). Two critical questions must be raised: What were exposures to xenohormones during critical windows of development, including the prenatal and pubescent periods, and what was the lifetime exposure to hormonally active parent compounds? Studies that look at contemporaneous measures of lipophilic metabolites of organochlorine compounds cannot resolve these questions. Moreover, measures of total PCBs cannot distinguish between active materials that are highly estrogenic and those which are antiestrogenic, and analytic studies of exposure need to be standardized for lipid adjustment (62).

**Need for Longer Term Studies**

Limited epidemiological studies have been conducted on the role of harmful or protective xenohormonal factors throughout the life cycle. No long-term comprehensive studies have yet been conducted or planned on large populations involving prenatal risk factors for breast cancer. In addition, biomarkers or metabolites of many quickly metabolized suspected agents such as some components of plastics, fuels, and aromatic materials cannot be directly measured in women long after exposure has ceased. Studies that look at current levels of lipophilic residues in cases of breast cancer compared to controls cannot resolve the issue of whether past exposures play a role in the development of the disease. The process of cancer alters metabolism in ways that are not well understood. Given the complex and competing roles of xenohormones, only long-term prospective studies that cover two generations will be able to resolve the issue of the relative roles of prenatal, pubescent, and subsequent exposures to harmful and beneficial xenohormones. Especially as potent forms of materials are excreted, it will be very important to obtain residues over the natural lifetime. Thus, the relative role of harmful or protective xenohormones and other factors such as Cox-2 inhibitors in affecting breast cancer vulnerability and in directly causing the disease is a matter that can only be resolved by studies that collect tissue for analyses through two generations.

Significant and unexplained elevated rates of breast cancer have been found across the United States, in places as diverse as Cape Cod, Massachusetts, and central Illinois. A recent report from San Francisco, California, like an earlier one from Long Island, New York, found that differences in the prevalence of so-called risk factors could theoretically account for all of the differences in the rate of breast cancer in that area (63). This study employed no individual measures, but modeled risk factors obtained in previous surveys of populations at risk of ovarian cancer compared to the population of San Francisco. In contrast, a national study of breast cancer mortality found that only 6% of cases accounted for only about half of the overall regional excess (64). Historically breast cancer incidence is about four- to sevenfold higher in the United States than in Asia. The risk of breast cancer increases when women migrate from those countries to the West. Those Asian–American women whose grandparents were born in America have 60% greater risk of breast cancer than those whose grandparents were born in Asia. Immigrants living in the West for a decade or longer have a risk of breast cancer 80% higher than more recent immigrants (50). The notion that there is something protective about being Asian is also borne out by a study that found no increased risk from elevated organochlorines in Asian–American women, but a two- to threefold risk in white and African–American women (57).

**Basic Research Issues**

We need to ask a number of basic research questions based on this proposed rethinking of risk factors. Why do girls who are taller and heavier at earlier ages have a greater rate of breast cancer? Could growth hormones in chickens, eggs, and dairy and meat products be involved in addition to greater amounts of calories overall? Why do women who lactate have a reduced risk of premenopausal breast cancer? Could lactation rid the body of potentially harmful, cancer-causing lipophilic agents in the mostly fatty breast tissue? For postmenopausal women, could cumulative buildup of harmful xenosterogens effectively void the added protection lactation provides for premenopausal women? Why do women who regularly consume alcohol have an excess risk of breast cancer? Why does alcohol contribute so dramatically to circulations of hormones in the blood? Why do women who exercise regularly have less breast cancer? Could their bodies contain lower levels of hormones, proportionally less fat, and less contaminants in fat that damage the breasts? Does a diet rich in beneficial xenohormones, such as genistien and omega-3-fatty acids, protect against breast cancer in Asian women? Would supplements or diets high in these foods prevent breast cancer? Does exposure to electromagnetic fields lower melatonin, which is a natural suppressor of breast cancer cell growth (65)? Do combustion by-products from fossil fuels (66) or from uncontrolled incineration of medical waste play any role in the increased rates of breast cancer in the urban environment (67)?

**Public Policy Questions**

It has been sardonically noted that one out of every four breast cancer cases among white women could be prevented if all white women had children before age 20, underwent menarche after age 14, had parents with no genetic or cultural predispositions to the disease, and had no benign breast conditions detected by a biopsy (12). In fact, most well-established risk factors for breast cancer cannot be changed in the present generation. Many of the risk factors involve exposures and circumstances that arise early in life; others entail matters over which women have little or no control as adults, such as the onset of menopause. Current proposed interventions to reduce breast cancer mainly focus on changing individual behaviors, including such self-imposed restrictions as lifelong administration of pharmaceutical agents or radical...
changes in diet, exercise regime, or reproductive behavior. However, some of the causes of breast cancer and related diseases can only be controlled by social and political action aimed at reducing the production, use, transport, and disposal of agents that directly or indirectly affect breast cancer risks.

The identification of contributing and vulnerability risk factors will provide a key missing component for fostering the promotion of policies that require public policy interventions. The public and private sectors could, for example, devise policies to prevent, restrict, or reduce exposure to agents in the household, workplace, and general environment that extend the duration and onset of breast growth or alter the hormonal environment. For these policies to succeed, experimental screening tests to identify xenohormones and other disruptive agents merit high priority. Once such test systems are in place, procurement policies as well as policies regarding workplace safety, education, and training and international trade can be modified to encourage the use of materials found to be less likely to alter hormone metabolism and extend cell growth.

Where there are significant risks of damage to the public health, we should be prepared to take action to diminish those risks even when the scientific knowledge is not conclusive, if the balance of likely costs and benefits justifies it (from Horton (68)).

The remaining central question for public policy is what risk factors give rise to 19 out of 20 cases of breast cancer. For more than 30 years, studies have repeatedly confirmed unmodifiable risk factors. These account for less than half of all cases. Probing for what available causes lurk behind breast cancer in San Francisco, Cape Cod, or anywhere else will be vital to solving the growing puzzle surrounding the disease and reducing its burden further.

For further information, see the World Resources Institute Website (69).

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