Medical Hypothesis: Xenoestrogens As Preventable Causes of Breast Cancer

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Changes in documented risk factors for breast cancer and rates of screening cannot completely explain recent increases in incidence or mortality. Established risk factors for breast cancer, including genetics, account for at best 30% of cases. Most of these risk factors can be linked to total lifetime exposure to bioavailable estrogens. Experimental evidence reveals that compounds such as some chlorinated organics, polycyclic aromatic hydrocarbons (PAHs), triazine herbicides, and pharmaceuticals affect estrogen production and metabolism and thus function as xenoestrogens. Many of these xenoestrogenic compounds also experimentally induce mammary carcinogenesis. Recent epidemiologic studies have found that breast fat and serum lipids of women with breast cancer contain significantly elevated levels of some chlorinated organics compared with noncancer controls. As the proportion of inherited breast cancer in the population is small, most breast cancers are due to acquired mutations. Thus, the induction of breast cancer in the majority of cases stems from interactions between host factors, including genetics and environmental carcinogens. We hypothesize that substances such as xenoestrogens increase the risk of breast cancer by mechanisms which include interaction with breast-cancer susceptibility genes. A series of major epidemiologic studies need to be developed to evaluate this hypothesis, including studies of estrogen metabolism, the role of specific xenoestrogenic substances in breast cancer, and relevant genetic–environmental interactions. In addition, experimental studies are needed to evaluate biologic markers of suspect xenoestrogens and biologic markers of host susceptibility and identify pathways of estrogenicity that affect the development of breast cancer. If xenoestrogens do play a role in breast cancer, reductions in exposure will provide an opportunity for primary prevention of this growing disease. Tests for estrogenicity could become critical screening tools with which to assess the potential health consequences of new and existing chemicals. *Key words:* aromatic hydrocarbons, breast cancer, chlorinated organics, genetic susceptibility, pesticides, xenobiotics, xenoestrogens. *Environ Health Perspect* 101:372–377(1993)

After years of puzzling, steady increases in breast cancer, public health researchers are rekindling interest in the role that exposure to xenobiotic agents, such as chlorinated organics and pharmaceutical agents, could play in the development of the disease. Do such substances increase the risk of this most common cancer in women by directly or indirectly altering estrogen production or metabolism? Do they activate or promote breast-cancer susceptibility genes (*1*)? Breast cancer is generally recognized to be determined primarily by total cumulative exposure to bioavailable estrogens (*2*). Could environmental chemicals that increase estrogen exposure by functioning as xenoestrogens explain some of the increases in breast cancer?

Although some of the recorded increase in breast cancer reflects improved detection (*3*), changes in known risk factors for the disease cannot completely explain recent patterns (*4*). A recent study that estimated age-specific rates of mammography from a Gallup Poll concluded that much of the recorded increase in incidence in the 1980s may be due to mammography, but that a sustained 1% annual increase in breast cancer mortality has occurred since the 1940s (*3*). Other studies have also documented increased mortality from breast cancer in a number of industrial countries (*5,6*).

About 40% of all cancers in women are hormonally mediated (*7*). Both estrogens and progestagens play critical roles in the development of breast cancer (*8*). This paper briefly reviews recent experimental and epidemiologic evidence on the critical and cumulative role of estrogens and xenoestrogens in the induction of breast cancer. We hypothesize that changes in exposures to xenoestrogenic substances may partly account for recent trends in breast cancer and present an opportunity for primary prevention.

Experimental Evidence

A number of lines of evidence attest to the ability of xenobiotic materials to affect estrogen production (*9*). Ovariectomy, which reduces endogenous hormones, inhibits the progression of chemically induced mammary tumors, whereas reintroduction of estrogen by implantation stimulates tumor development. Moreover, rat mammary cancers depend on both late and early exposure to estrogen and prolactin (*11*).

Experimental studies indicate that estradiol metabolism proceeds primarily via two mutually exclusive pathways, each of which is affected by xenobiotic exposures: pathway I to 2-hydroxyestrone (2-OHE1), which has minimal estrogenic activity and is nongenotoxic, or pathway II to 16α-OHE1, a fully potent estrogen which is also genotoxic (*12*). Breast cancer risk appears to be linked with these two pathways. Substances that elevate pathway II or inhibit pathway I increase risk, whereas those that inhibit pathway II or elevate pathway I decrease risk. Thus, dimethyl benzanthracene (DMBA), benzo[*a*]pyrene (BaP), oncogenes, and tumor virus exposure inhibit pathway I and also induce mammary tumors (*13*). Dietary supplements that increase pathway I, such as indole-3-carbinol, also decrease mammary tumor incidence (*14*), but those that induce pathway II, such as alcohol, tend to increase carcinogenic response (*10,15*). In addition to affecting pathway II, alcohol consumption has been shown to induce P450IIE and decrease P4501A1, subfamilies of enzymes key to the metabolism of other potential carcinogens (*15*).

As to the role of dietary factors in estrogen production, a number of studies indicate that both fat and fiber intake modulates estrogen metabolism. Linoleic and arachidonic acids increase pathway II (*12*). A high-fiber diet, along with greater physi-

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cal exercise, reduces enterohepatic resorption of fecal estrogens (*16*). Severe caloric restriction results in major increases in pathway I and reductions in pathway II (*17*).

A variety of *in vitro* and *in vivo* studies have documented the estrogenicity of some lipophilic, bioconcentrated xenobiotics; that is, their ability to stimulate estrogen and function as xenoestrogens (Table 1). Estrogens promote breast cell proliferation (*18*) and hypertrophy of other secondary sex organs (*19*). Similar effects have been observed in fish, birds, and wildlife (9). Xenoestrogenic substances include several lipophilic, persistent compounds for which human, food chain, and wildlife exposures have been widespread (*20*). These chemicals include a number of chlorinated organics, such as *o,p'*-DDT, an isomer of the pesticide DDT, chlordecone, heptachlor, and other pesticides, polychlorinated biphenyls (PCBs), triazine herbicide, and a number of polycyclic aromatic hydrocarbons (PAH), compounds derived from petroleum products, fossil fuels, and products of incomplete combustion. In addition, some pharmaceutical agents such as diethylstilbestrol (DES) are direct estrogens, and others, such as tamoxifen, mimic estrogen in premenopausal women but block estrogen in postmenopausal women (*21*). Still other pharmaceuticals, such as cimetidine, inhibit pathway I and stimulate breast cell proliferation (*22*). Animals exposed to ambient levels of commonly encountered compounds one at a time, such as Aroclor 1254, a PCB, showed no adverse effects. But animals dosed with mixtures of ambient levels of commonly encountered groundwater contaminants, including PCBs and ubiquitous viruses, developed a variety of adverse effects on growth and reproduction (*23*).

A number of xenoestrogenic compounds induce or promote breast cancer experimentally (*24*). Primary carcinogenesis may also occur with other xenobiotics because human breast epithelial and fibroblastic cells metabolize them to carcinogenic electrophiles (*25*). Table 2 summarizes the research on mammary carcinogenicity of several important, widely used toxic substances. These include *o,p'*-DDT, some isomers of PCB, benzene, and several PAHs, including methylcholanthrene, dibenz[*ah*]anthracence, and DMBA (*26–28*). PAHs produce increased intracellular oxidation and chromosomal breaks or gene rearrangements (*29*).

Atrazine is of special interest, as it is a triazine herbicide that is one of the most commonly used pesticides in the United States today, and it is widely found in groundwater (*30*). Atrazine is a stable compound that is retained in the abdominal fat of chickens for a week following 1 week of feeding (*31*). It induces exceptionally rare breast tumors in male animals and also produces reproductive organ tumors (*32*) and endocrinological effects.

Table 1. Experimental evidence on the estrogenicity of some chlorinated organics

Chemical	*In vivo* evidence	Reference	*In vitro* evidence	Reference
o,p'-DDT	Initiated implantation and maintained pregnancy in rats	Johnson et al., 1992 (*67*)	Inhibits the binding of [^{3}H]estradiol to rat uterine cytosolic estrogen receptor	Nelson, 1974 (*68*)
o,p'-DDT	Uterotropic (causes increased uterine weight) in rats	Welch et al., 1969 (*69*)	Inhibits the binding of [^{3}H]estradiol to rat uterine cytosolic estrogen receptor	Nelson, 1974 (*68*)
Methoxychlor	Initiated implantation and maintained pregnancy in rats	Johnson et al., 1992 (*67*)		
Chlordecone (kepone)	Initiated implantation and maintained pregnancy in rats	Johnson et al., 1992 (*67*)		
ß-Hexachloro-cyclohexane			Induction of cystosolic progesterone receptor; redistribution of estrogen receptors	Coosen and Van Velsen, 1989 (*70*)
PCBs			Estrogen receptor binding to probes	Korach et al., 1988 (*71*)
Kepone (chlordecone), heptachlor, chlordane, Aroclor 1221			Enhanced proliferative potency in human breast estrogen-sensitive MCF7 cells	Soto et al., 1992 (*19*)
Atrazine			Hormone release increased	Ghinea et al., 1988 (*72*)

Table 2. Experimental evidence on mammary carcinogenesis of some chlorinated organics

Chemical	Animal evidence	Reference
Organochlorines		
DDT	Accelerator of mammary tumors in male mice treated with 2-acetamidophenanthrene	Scribner and Mottet, 1981 (*73*)
Triazines Atrazine	Increased incidence of mammary tumors in male rats (750 ppm for 126 weeks)	Pinter et al., 1990 (*32*)
Benzene	Breast cancer, oral and respiratory routes	Maltoni et al., 1989 (*74*)
Polycyclic aromatic hydrocarbons		
Benzo[*a*]pyrene	Mammary tumors, gastrointestinal route	Huggins and Yang, 1962 (*75*)
Dibenz[*ah*]anthracene	Mammary tumors, gastrointestinal route	Snell and Steard, 1962 (*76*)

Epidemiologic Evidence

Two recent epidemiologic studies have highlighted the importance of pre-natal exposures to estrogen for breast cancer. One investigation found that women born to mothers with pre-eclampsia, and therefore lower estrogen levels during pregnancy, had significantly reduced risks of developing breast cancer compared with controls. In this same analysis, women born to mothers with elevated estrogen during pregnancy sustained an increased risk of breast cancer that was not statistically significant but may have biological importance (*33*).

A second study corroborates the role of prenatal exposures to estrogen. Dizygotic twins, whose mothers generally have higher levels of estrogens, have higher rates of breast cancer. Among all twins, the odds ratio associated with one of the twins being male (1.54) was higher than those associat-

Table 3. Case–control studies on chlorinated organics and breast cancer

Reference	Matching; confounding	No. of cases/ controls	Analytes	Relative risk (odds ratio)
Albert et al. 1982 (*77*) (tumor vs. normal mammary tissue)	None	8/7	DDT,[a] HCH,[a] dieldrin, heptachlorepoxide	—
Wassermann et al., 1976 (*78*) (tumor vs. normal mammary tissue)	None	9/5	DDT,[a] DDD,[a] PCB,[a] HCH, dieldrin, heptachlorepoxide	—
Unger et al., 1984 (*48*) (biopsy)	No matching; age	14/21	DDE, PCB	
Unger et al., 1984 (*48*) (autopsy)	No matching; age	18/35	PCB	
Falck et al., 1992 (*49*)	No matching; age, height, weight, smoking	20/20	DDE,[b] DDT, PCB,[b] heptachlorepoxide, oxychlordane, *trans*-nonachlor, HCB, b-HCH	
Mussalo-Rauhamaa et al., 1990 (*50*)	No matching; age, parity, weight, height, occupation, smoking, fish meals	44/33	DDT, PCB, HCB,HCH,[b] heptachlorepoxide, chlordane, *trans*-nonachlor, PAH	10.5 (>0.1 ppm)
Wolff et al., 1993 (*51*)	Age, menopausal status, day of cycle, enrollment date, body mass, age at menarche, parity, family history, past benign disease, lactation, smoking, alcohol use, race	58/171	DDE,[b] PCB	4 (10th–90th percentile)

HCH, hexachlorocyclohexane; HCB, hexachlorobiphenyl.
[a]Albert et al. (*77*) and Wasserman et al. (*78*) found differences between malignant and normal breast tissue for these residues.
[b]Associated with elevated risk.

ed with both twins being female (1.3) and was highest in premenopausal women with twin brothers (2.88) (*34*). This may be due to the fact that developing, hormonally affected organs in sisters of twin brothers are exposed to relatively more circulating prenatal estrogens than are twin sisters. Prenatal imprinting may prime estrogen receptors for subsequent response or provide irreversible programming of the distribution of cytochrome P450s and other of the terminal enzymes of the microsomal and mitochondrial mixed-function oxidase, electron transport chains.

Most of the known risk factors for breast cancer, which at best account for 30% of cases (*2*) are linked with total lifetime exposure to reproductive hormones (*35*). Aside from genetics and radiation in premenopausal breast cancer, these risk factors include age, age at menarche, menopause, and first full-term pregnancy, total calorie intake, family history, height, radiation exposure, and alcohol intake (*36*). Artificial reduction of hormones by ovariectomy before age 35 reduces human breast cancer risk (*36*).

Diet influences estrogen production in various ways. A diet of proportionally higher total calories relative to body mass can also alter the metabolism of estrogen in the gut and stimulate earlier onset of menses. However, obese, premenopausal women who are amenorrheic have reduced risks of breast cancer, whereas obese postmenopausal women have higher risks, presumably due to the ability of body fat to enhance production of estrogens after menopause when ovarian production of estrogen diminishes rapidly (*2*). Severe restriction of caloric intake appears to reduce the risk of breast cancer (*37*), possibly by delaying the onset of menses or otherwise reducing total lifetime estrogen exposure.

The role of dietary fat for breast cancer remains the subject of a lively debate and inconsistent results. A meta-analysis of 12 case–control studies reported that the risk of breast cancer increased with increasing dietary fat and included some studies with more than a twofold difference (*38*). Others have found no such association (*39*).

Direct epidemiologic evidence linking chlorinated organics to breast cancer ranges from suggestive geographic and cross-sectional mortality analyses to case–control studies. A recent analysis of chemical plant workers found more than a twofold increase in breast cancer in female workers exposed to dioxin contamination (*40*). Elevated breast cancer rates were also detected in an analysis of women exposed to extensive environmental contamination with PCBs in Japan (*41*). In contrast, other studies have been negative (*42,43*).

Geographic and other large-scale analyses have suggested a link between breast cancer and PAH or chlorinated organic compounds but have not involved any direct measures of exposure (*16*). Significantly elevated rates of breast cancer have been detected in one area of Minnesota where water was contaminated with PAHs (*44,45*). Women who work in the chemical industry (*46*) or who live near hazardous waste sites are also reported to have higher rates of breast cancer (*47*). Another study reported a temporal association between a decrease in population exposure to chlorinated organics and a reduction in breast cancer mortality rates (*16*).

As Table 3 reveals, most of the negative analytic studies have involved fewer than 10 cases and have had only about a 30% chance of detecting a twofold difference in risk (*48*). Several more recent studies have provided evidence that chlorinated organics are linked to breast cancer. In one study, the breast fat of women with cancer at biopsy had about 40% more of some chlorinated pesticides such as metabolites of DDT and elevated levels of PCB (*49*). About 50% more hexachlorocyclohexane (*50*) was detected in pooled blood from breast cancer cases compared to a pooled reference group, controlling for age and parity.

Further resolution of the role of chlorinated organics comes from a well-designed study that matched on several factors and adjusted for a number of confounders. This recent nested case–control study of 58 prospectively gathered cases was drawn from a cohort of 14,000 women. Women at the 90th percentile of DDE in serum had a fourfold greater risk of breast cancer compared to those at the 10th percentile (*51*). PCB levels also differed, but this difference was not statistically significant. Two other case–control studies are also germane involving ovarian cancer, which is also hormonally mediated. A hospital-based case–control study in Italy detected a significant link between herbicides and ovarian cancer but could not pinpoint specific exposures (*52*). A population-based case–control study which provides better characterization of exposure and controls

for relevant reproductive risk factors notes that women exposed to chlorinated organic triazine herbicides through farmwork for 10 or more years have a relative risk of 2.7 for ovarian cancer (*53*).

Hypothesis

A variety of experimental and human evidence indicates that the greater the total lifetime exposure to bioavailable estrogen, the greater the risk for breast cancer. In light of the pivotal role of estrogen, we hypothesize that exposure to some xenoestrogens elevates endogenous hormone levels, especially 16α-OHE1, which stimulate breast cell proliferation and thereby induce or promote breast cancer. Xenobiotic compounds could alter bioactive estrogen or progesterone in breast cancer cases or otherwise induce mammary carcinogenesis through the P450 enzymes. Those with genetic susceptibility to breast cancer might be exquisitely sensitive to the proliferative effects of xenoestrogenic substances in the environment.

Xenoestrogenic compounds may work through several estrogen-related mechanisms or through other mechanisms unrelated to estrogen (Fig. 1). Environmental chemicals may be directly estrogenic, as is *o,p'*-DDT. Or they may alter estradiol metabolism, or otherwise enhance the production of 16α-OHE1 (pathway II) or reduce the production of 2-OHE1 (pathway I), as occurs with some drugs such as cimetidine. In addition, potentiating factors such as alcohol and fat may affect estrogen hydroxylation. Other breast carcinogens appear to operate completely outside of estrogen pathways as direct carcinogens. For example, fluoroscopic radiation induces mammary carcinoma experimentally and in humans, probably by direct stimulation of proliferating ductal cells or direct mutation of stem cells.

Whatever the pathway to breast cancer, genetic factors are ultimately involved in the expression of this highly heterogenous disease. Younger women are more affected by inherited genetic factors, as hereditary breast cancer accounts for 36% of breast cancer cases ages 20–29, but only 1% of cases over age 80 (*54*). In some families with the rare, autosomal dominant Li-Fraumeni syndrome (*55*), a high breast cancer risk is due to the inheritance of a specific cancer-predisposing mutation on chromosome 17q21 (*56,57*). Results of a recent population study suggest that more than 6.5 women per 1000 with breast cancer are carriers of another inherited breast cancer-predisposing mutation in a series of codons on chromosome 17 (*54*).

As the proportion of inherited breast cancer in the population is small (*58*), most breast cancers result from acquired mutations, possibly stemming from xenoestrogens or from environmental carcinogens that affect pathways other than estrogen. This hypothesis suggests that it is important to study genetic–environmental interactions to identify environmental factors that influence gene expression in the great majority of acquired mutations.

Two lines of evidence are pinpointing the location of cancer-predisposing genes on chromosome 17 in both inherited and somatic mutations for breast cancer: gene linkage studies in families with multiple affected members and allelic composition studies comparing tumors with normal tissues for loss of heterozygosity (Fig. 1). Two genes have recently been implicated in the development of hereditary breast cancer, the tumor-suppressor gene p53 (*56–60*), which maps to chromosome 17pl3.1, and the breast-cancer-suppressor gene BRCA1 (*61*), which was originally identified by linkage to the anonymous DNA marker D17S74 at 17q2l (*62*) and appears to be involved in the largest proportion of inherited breast cancer. For noninherited breast cancer, the role of xenoestrogenic or xenobiotic exposures for oncogene activation or gene suppression needs to be carefully evaluated.

Discussion

How can we explain the fact that the generation of women who had their children earlier in life and had more of them now have higher rates of breast cancer? Obviously, known risk factors do not completely account for breast cancer patterns in industrialized countries (*4*). The great preponderance of these factors, such as early age of menses, late age of menopause, reproductive history, and caloric intake relative to body weight, can be linked to total lifetime exposure to bioavailable estrogen. We need to identify xenobiotic factors that directly or indirectly increase estrogen exposure. A number of studies are suggested by this theory. Investigations of populations with differing rates of disease and xenoestrogen exposures will permit us to test this hypothesis, as will analyses of archived materials from varied populations. A major series of case–control studies in countries with differing breast cancer rates and chemical exposures should further assess the role of xenoestrogenic materials by assaying markers of exposure to suspect xenoestrogens and early markers of biologic effect. Special attention needs to be paid to the mechanisms by which environmental exposures, including xenoestrogens, might activate oncogenes or suppress other genes, teasing out the interaction between genetic susceptibility and environmental factors. In addition, laboratory studies in human cell culture and *in vivo* systems of suspect xenoestrogenic materials should be expanded to screen chemicals for estrogenicity and to identify mechanisms by which these substances could affect estrogen metabolism or otherwise promote the development of breast cancer. Preliminary *in vitro* work has found that several pesticides enhance the production of the genotoxic pathway II, 16α-OHE1, and reduce the yield of the nongenotoxic pathway I, 2-OHE1.

The xenoestrogenic hypothesis offers a possible resolution to several anomalies in breast cancer research, including some inconsistent results about dietary fat and breast cancer. Fat per se may be less important than xenoestrogenic contaminants in fat at different stages in women's lives. As to the postmenopausal period, one recent study found that 4 years after treatment,

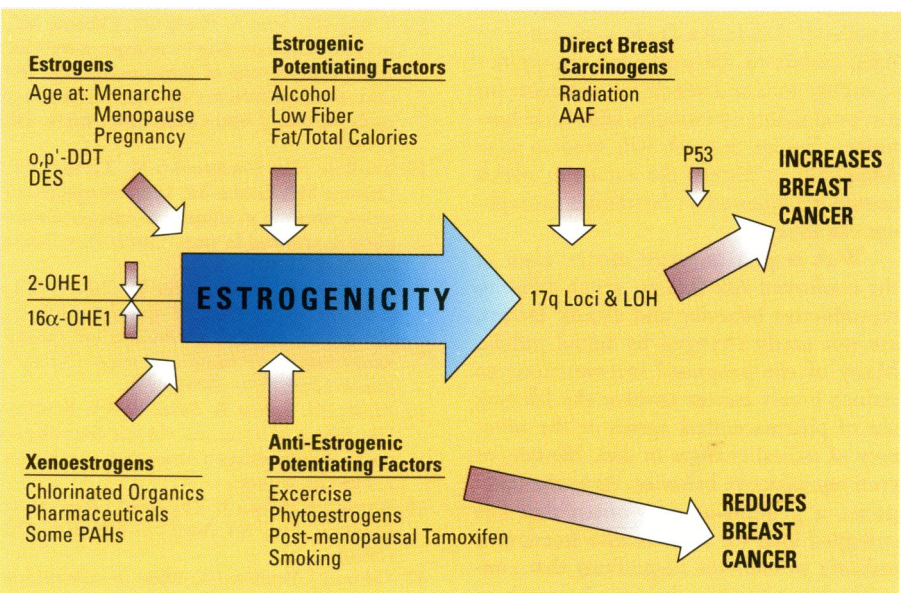

Figure 1. Hypothesized pathways to breast cancer. OHE1, hydroxyestrone; LOH, loss of heterozygosity.

breast cancer recurred in postmenopausal women with positive estrogen-responsive receptors who ate diets high in fat, total fat intake, and saturated and polyunsaturated fats, as assessed at time of diagnosis (*63*). We need to determine whether bioaccumulated lipophilic, xenoestrogenic substances, such as PAHs and chlorinated organics, are elevated in these women, as well as whether saturated animal fats bioconcentrate higher levels of such compounds than do polyunsaturated vegetable fats.

This hypothesis also may account for one of the discrepancies in cancer that was first noted by the distinguished Danish researcher Clemmensen. Commonly referred to as Clemmensen's hook, the discrepancy occurs in the relationship between age and breast cancer incidence for several countries. Incidence of breast cancer rises monotonically with age up to about age 45, after which the rate of increase forms a hook and levels off or declines for about 10 years and then resumes an increasing, but more modest slope (*64*). The ages of this plateau correspond to the period of perimenopause, when the ovaries begin to produce less estrogen and progestin. It is tempting to speculate that the renewed surge in breast cancer after menopause, especially in obese women, might be linked with xenoestrogens and with the production of endogenous estrogens, which would be greatest in those with proportionally more body fat.

A recent series of studies on the possible link of environmental hormones with male reproductive disorders bears mention (*65*). Reported disorders of the male reproductive tract, including reduced sperm counts and testicular cancer, have increased over the past several decades (*66*). Could prenatal exposures to xenoestrogens be involved? Evidence from a number of fields points to the profound importance of endogenous and xenobiotic materials for the production of estrogen and other hormones. Future research will need to span disciplines to discern the extent to which human activities affect hormones throughout our lives.

With respect to breast cancer, most of the confirmed risk factors, which relate to reproductive behavior and dietary factors, are not easily changed by social policy. Many of the proposed interventions to reduce breast cancer involve the lifelong use of pharmaceutical agents or the advocacy of radical changes in diet, lifestyle, or even reproductive behavior. As to the latter point, a generation of women that has struggled long for reproductive freedom is unlikely to embrace suggestions that constrain reproductive choices. Research to pinpoint preventable causes of breast cancer is critically needed. If xenoestrogens do play a role in breast cancer, reductions in exposure will provide an opportunity for primary prevention of this growing disease.

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