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Xenoestrogens may be the cause of high and increasing rates of hormone receptor positive breast cancer in the world

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SUMMARY

Breast cancer rates are higher in the Western or industrialized world when compared to Africa or Asia. Within the developing world, breast cancer rates are higher in urban areas where people have a more Westernized lifestyle. In addition, there has been a steady increase in the breast cancer incidence across the world. It is already a known fact that the proportion of hormone receptor positive breast cancer cases is higher in the developed world. Evidence from developed countries also shows that most of the increase in breast cancer incidence has been due to an increase in hormone receptor positive breast cancer. Most of the breast cancer incidence can be explained by environmental factors and genetic causes. However, all known risk factors of breast cancer can explain only 30–50% of breast cancer incidence. In the past decade, a number of compounds that affect female hormone homeostasis have been discovered. These xenoestrogens have been shown to cause breast cancer and also induce the expression of hormone receptors in vitro and in vivo. Given the high use of substances containing xenoestrogens in developed regions of the world and their increasing use in urban parts of the developing world, xenoestrogens could be the important cause of high and increasing rates of hormone receptor positive breast cancer across the world. New research in the area of mammary stem cells provides added indication of the probable time period of exposure to xenoestrogens with chronic exposure later in life leading to hormone receptor positive breast cancer and most probable reason behind increasing breast cancer incidence.

Introduction

Breast cancer is the most common malignancy among women in most developed and developing regions of the world with nearly a million new cases each year. It accounts for nearly 21% of all cancers among women worldwide [1]. The incidence rates of breast cancer are high in North America, Northern, and Western Europe, intermediate in South America, and Southern Europe and low in Africa and Asia. The age-standardized (world population) incidence rates of breast cancer per 100,000 women were over 100 in Montevideo, Uruguay in South America (114.9), among Non-Hispanic Whites in California, North America (109.6) and among Hawaiians, Hawaii in Oceania (101.3). The lowest incidence rate (age-standardized) of breast cancer was seen in The Gambia in Africa (7.0) [2]. Overall, the distribution of breast cancer rates closely resembles the distribution of indicators of "affluence". Prevalence of carriers of the major susceptibility genes (BRCA1 and BRCA2) in the general population is low, and their differential distribution around the world can hardly account for much international or inter-ethnic variation in risk. Most of the differences in incident rates are therefore a consequence of the different environmental exposures, and indeed there are quite marked changes in risk following migration, particularly if this takes place at a young age [3].

In addition to differences in geographical variations in incidence of breast cancer, there have also been variations in time. Incidence rates of breast cancer have been increasing in most countries, and the changes are usually greatest where the rates were previously low. There has been an approximate increase of about 0.5% annually in breast cancer incidence in the world and it has been estimated that this would result in 1.35 million new cases in 2010 [3]. However, cancer registries in China are recording annual increases in incidence of over 5% which is similar to many other places in East Asia. Still assuming a conservative estimate of 3% increase in incidence rates in east Asia, the figure for 2010 would be 1.45 million new cases, which is a 82% increase on the figure in 1990 [3]. Researchers have postulated that changes in the age of childbearing, alterations in the average ages of menopause and menarche, and/or the widespread use of oral contraceptives and hormone replacement therapy might have contributed to the increasing incidence [4]. However, among the causes of breast cancer, hereditary factors account for only 5–10% of risk and the above mentioned environmental exposures account for an additional 30–50% of risk [5]. Other suspected environmental factors are possibly related to the poorly-defined proportion of breast cancer risk

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which is also possibly the cause of temporal changes in breast cancer incidence.

In addition to differences in incidence rates, there are also differences in distributions of subtypes of breast cancer based on the estrogen receptor (ER) status and progesterone receptor (PR) expression of tumors. Based on receptor types there are four types of breast tumors: ER+/PR+ or hormone receptor positive (HR+), ER+/PR−, ER−/PR+, ER−/PR− or hormone receptor negative (HR−). Within the United States, there are differences in HR between races with Caucasians having greater prevalence of HR+ breast cancer than other races [6,7]. In addition, studies in other countries which have lower incidence rates of breast cancer have reported lower proportions of HR+ breast cancer [8]. It is quite possible that the higher prevalence of ER positivity may be a characteristic of populations at increased risk of breast cancer [9]. Apart from differences in space, a review of available information of ER status from US SEER has clearly shown an increase in the proportion of ER positive tumors with time while the proportion of ER negative tumors has remained constant. In fact it has been concluded that most of the increase in incidence of breast cancer in the USA has been due to an increase in the incidence of ER positive breast cancer [10].

Interest in ER/PR status in the past was mainly due to differential response of patients to hormonal therapy with HR+ patients having the best response to hormonal therapy and HR− patients having the worst response [11]. However, studies soon began looking into other aspects of breast cancer based on hormone receptor status (HRS) and concluded that tumors with different HRS might in fact be different subgroups of breast cancer [12]. If we look at differences in risk factors based on HRS, it is seen that the risks associated with HR+ tumors are mostly related to reproductive factors such as nulliparity, early age of menarche and late age of menopause, use of hormone replacement therapy etc. [13,14]. These are factors which increase a woman's lifetime exposure to estrogen. On the other hand, the risk factors most closely associated with HR− tumors are independent of hormonal exposure such as smoking, family history and radiation exposures [13,15]. Thus, this and the rest of the evidence above points out that the risk factor that is causing high and increasing risk of breast cancer across the world is probably an environmental factor that is hormonal in nature and is linked to development and affluence.

Hypothesis

ER and PR are the two main hormonal receptors regulating the growth and differentiation of the breast. PR expression is under the control of ER expression [16] and progesterone is in general protective for breast cancer due to the effects of differentiation it causes in the breast tissue [17]. This implicates estrogen as the main carcinogen acting on the breast [18]. Reproductive factors have changed with development around the world with women in developed areas of the world having earlier menarche due to improved nutrition, later age of first childbirth, lesser number of children, lesser duration of lactation, later menopause and use of hormone replacement therapy (HRT). These factors have increased the lifetime exposure of a woman to estrogen and might be responsible for an increase in HR+ breast cancer. However, estimates show that these factors along with genetic causes explain a maximum of 50% of the breast cancer risk [19,20] which points towards other environmental factors that may have an important role to play in increasing the risk of HR+ breast cancer.

One of the probable important environmental factors that can affect breast cancer risk is chemicals present in the environment that affect the endocrine system of the body. These chemicals act like estrogen in the body or disrupt the normal metabolism of natural estrogen and thus act as carcinogens (Table 1) [21]. These chemicals were named endocrine disrupting chemicals (EDCs), exogenous estrogens or xenoestrogens. These xenoestrogens (we will stick to this terminology in the rest of the paper) were serendipitously discovered by researchers in Tufts University in 1991 when they found that a chemical leaching from polystyrene tubes was causing breast cancer cells to grow in the absence of estrogen. This chemical was found to be *p*-nonylphenol, a common additive in plastics [22]. Increasing curiosity and further research by Tufts University researchers identified certain pesticides that caused breast cancer cells to proliferate in tissue cultures [23]. In another 3 years, a number of other compounds had been discovered that acted like estrogens when in contact with breast cancer cells [24–26]. Animal studies followed in vitro studies and in 2005, researchers from Texas showed an increased risk of breast cancer among mice exposed to 4-nonylphenol (4-NP) compared to mice exposed to equivalent doses of estradiol. This increased risk was due to stimulation of estriol production in liver by 4-NP [27].

In the ensuing years there have been a number of studies that have looked at circulating levels and adipose tissue levels of xenoestrogens in the body and association of these levels with breast cancer [28–30], with most of these studies finding weak associations or equivocal results [31]. One of the reasons for this might be the loss of power occurring from looking at associations of xenoestrogens with all breast cancer when xenoestrogens might be the cause of specific subtypes of breast cancer. Other reasons might be the presence of a number of xenoestrogens and their interaction with each other which was not taken into account [31], the use of populations where exposure to xenoestrogens is ubiquitous which reduces power due to the absence of an unexposed population or the absence of correct methods to assess xenoestrogen exposure [32]. However, better assessment methods have shown increased association between xenoestrogens and breast

Table 1
Common chemicals linked to breast cancer.

Chemical class	Potential sources	Example chemical
Pthalates	Plastic, nail polish and other cosmetics	Dibutyl pthalate
Alkylphenols	Detergent, plastic, pesticide formulations	Nonylphenol
Flame retardants	Furniture foam and stuffing, carpets and drapes, electronic equipment (TVs, computers)	Polybrominated diphenyl ether (PBDE 47)
Polycyclic aromatic hydrocarbon (PAHs)	Stoves and heaters, cigarette smoke, outdoor air pollution, auto exhaust, combustion sources such as fireplaces	Benzo(*a*)pyrene
Polychlorinated biphenyls (PCBs)	Older electrical equipment	PCB 52
Banned pesticides	Historical pesticide use in/near the home	DDT, dieldrin, chlordane
Currently used pesticides	Recent pesticide use in/near home	Chlopurifos, permethrin
Other phenols and miscellaneous	Disinfectants, polycarbonate plastics, cosmetics	*o*-Phenyl phenol, bisphenol-A, parabens

Adapted from Ref. [21].

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cancer such as the study in Spain looking at total effective xenoestrogen burden (TEXB). This study found an increased risk of breast cancer among postmenopausal women with highest levels of TEXB-α [33]. Some studies have also found credible evidence of there being gene-environment interactions between xenoestrogens like PCBs and the cytochrome enzyme system [34].

Thus, recent evidence clearly links xenoestrogens to breast cancer and given the associations of xenoestrogen use and environmental presence with development in the modern world we hypothesize that women in developed countries and urban areas of developing countries are having increased exposures to xenoestrogens which is causing high and increasing rates of breast cancer and more specifically HR+ breast cancer. This idea as a hypothesis has not been put forth in the past. The implications of this hypothesis, if proven epidemiologically and at the molecular level, could lead to primary prevention efforts that would reduce the exposure of women to xenoestrogenic compounds and reduce the incidence of breast cancer worldwide.

Evaluation of the hypothesis

Broadly xenoestrogens can be divided into long acting and short acting. Long acting chemicals are lipid soluble and are capable of remaining in the body for decades in conjunction with adipose tissue. Some of these chemicals, also known as persistent organic pollutant or POPs consist of a number of pesticides and insecticides such as DDT, hexa-chloro-hexane (HCH), PCBs etc. [33,35]. Being sequestered in the adipose tissue, these chemicals leach into the circulation resulting in constant minute exposure of the entire body to these chemicals over time [36,37]. Short acting chemicals are water soluble and are present in many articles of everyday use including plastics, bicarbonate bottles, cosmetics, food preservatives etc. Although most of these chemicals, such as bisphenol-A and parabens, are excreted out of the body rapidly, continuous exposure to them might result in constant levels of these chemicals in the body making them equally harmful.

Although there is no direct data showing the consumption patterns of xenoestrogens across the world, we can infer to their consumption based on data available for pesticide use across the world. Pesticide use in the world has been rising in the past decades mainly due to pressures on agriculture to produce more food for the growing population of the world [38]. While most of the pesticide use in developed countries has evolved on to the use of more specific products, outdated pesticides that persist in the environment are still used in developing countries. These are produced by companies in the developed world who no longer can sell them in developed countries and so continue to sell them in the developing world either through subsidiaries or local tie-ups [38].

While pesticides mostly belong to the category of long acting xenoestrogens, there has been an exponential increase in the use of short acting xenoestrogens mainly due to increasing use of plastics in all walks of life. It is estimated that almost 1 trillion plastic bags are consumed each year around the world with the US using around 380 billion plastic bags out of which approximately 100 billion are shopping bags [39]. North America and Western Europe account for 80% of plastic bag use in the world and a quarter of those bags are now made in Asia [40]. Apart from bags, plastic use is seen increasingly in all spheres of life now including but not limited to food and drink containers, electronics, medical products etc. Short acting xenoestrogens are also seen in other categories of products such as food preservatives, cosmetics, detergents etc. [41–43]. Since in the modern world use of all the above products often accompanies development, developed countries show high production and use of them in everyday life with a similar trend being seen in developing countries, mainly in urban areas.

At the molecular level, a number of these xenoestrogens have been found to act through the estrogen receptor. It has been shown that bisphenol-A (BPA) acts through the same response pathway as natural estrogen at high as well as low doses [44–46]. Other xenoestrogens such as nonylphenol also directly stimulate ER in in vitro studies [47]. Studies have also reported that drugs like tamoxifen might increase the agonistic effects of xenoestrogens on mutant ERs which might have implication related to drug refractoriness and drug resistance [48]. A few studies have also demonstrated that xenoestrogens like DDT and its metabolites increased growth of ER+ breast tumors with one study refuting this hypothesis [49–51].

Thus the hypothesis that xenoestrogens are the cause of high and increasing incidence of HR+ breast cancer across the world implies that xenoestrogens are related to the occurrence of a specific subtype of breast cancer. This hypothesis also predicts clearly that urban areas in developing countries would have higher incidence of breast cancer and HR+ breast cancer than rural areas. It also predicts that most of the increase in breast cancer incidence in developing countries is due to an increase in HR+ breast cancer and the urban areas of developing countries would have higher rates of increase in HR+ breast cancer than rural areas. A well planned study looking at incidence rates of breast cancer and HR+ breast cancer from a population-based cancer registry in a developing country would be able to prove these predictions emanating from the hypothesis.

Discussion

Not only is exposure to xenoestrogens significant but the period in the lifetime of an individual when a woman gets exposed to estrogens or xenoestrogens is also significant [52]. If we look at the pattern of distribution of HR+ tumors by age we find from US SEER data that HR+ positive tumors tend to occur later in life compared to HR− tumors [53,54]. Also, in developing countries where HR− tumors are more common, women tend to be younger when they develop breast cancer [55]. Further insight into when and how xenoestrogens might be acting to increase breast cancer risk comes from one of the newest areas of study in breast cancer – mammary stem cells.

Stem cells, more specifically somatic stem cells, are found in all parts of the body and are responsible for normal tissue renewal [56]. To fulfill this purpose stem cells perform asymmetric divisions in which they generate one cell identical to it and another which is more committed towards a certain differentiation pattern. Thus stem cells can maintain their population as well as produce transit cells or intermediate cells [57]. Breast is an organ that undergoes repeated cycles of growth and apoptosis throughout the lifecycle of a woman [58]. A pool of mammary stem cells has been clearly shown to be present in the breast that provides this regenerative capacity [59].

The hypothesis that cancer has its origins in stem cells is well-established [60,61]. Presence of stem cells in many hematopoetic malignancies, solid tumors and breast tumors has further confirmed this hypothesis [62–64]. Although a clear population of stem cells in breast is yet to be defined a putative breast tumor stem cell like population has been identified which is defined by the presence of two cell surface markers – CD44 and CD24 with these cells being CD44+/CD24− [64].

Research in humans and mice have pointed out that initial cells during early development of mammary tree do not have estrogen receptors [65,66]. These early stem cells start out as ER− cells and differentiate to form ER+ cells post-natally that later on leads to the development of breasts during puberty under the influence of estrogen [65]. A model has been proposed about cancer develop-

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Table 2
Subtypes of breast cancer based on stem cell type of origin.

Cancer type	Type 1	Type 2	Type 3
Cell of origin	Stem cell	Stem cell	ER+[a] progenitor
ER[a] expression	Negative	Heterogeneous[d]	Positive
Histology	Undifferentiated. Basal and luminal markers present,	Intermediate differentiation	Differentiated
Prognosis	Poor	Intermediate	Luminal markers only. Good.
Risk from HRT[b]	Unchanged	Limited	Increased
Efficacy of SERMs[c] in prevention	None	Limited	High
Probable period of exposure to xenoestrogens	Early in life, most likely in intrauterine period	Early to intermediate	Intermediate to late and prolonged

Adapted from Ref. [67].
[a] ER – estrogen receptor.
[b] HRT – hormone replacement therapy.
[c] SERMs – selective estrogen receptor modifiers.
[d] ER+ cells represent 10–80%.

ment from stem cells based on ER status. This model divides stem cells into three types with the most primitive cell being ER− and giving rise to ER− tumors. The intermediate stem cells have a more heterogeneous division of ERs and show limited response to SERMs and intermediate prognosis. The stem cells farthest from the primitive stem cells in this hierarchy are the ER+ progenitor cells which show maximum differentiation and good prognosis (Table 2) [67].

Thus it seems that risk factors that produce HR− cancer affect the primitive stem cells early in life, most likely in the intrauterine period while risk factors that produce HR+ cancer affect the intermediate or progenitor cells later in life as is also apparent from the development of HR+ tumors later in life [53,54]. This implies that it is long term exposure of a woman throughout the life to xenoestrogens that causes an increase in HR+ breast cancer. At the molecular level this seems quite plausible since most long term xenoestrogens get sequestered in the adipose tissue and are released gradually into circulation [36,37] while most short term xenoestrogens are water soluble and result in consistent exposure in spite of constant excretion from the body. This exposes a woman to low doses of both types of xenoestrogens over time and thus increases the risk of HR+ breast cancer.

It has been known from previous studies looking at the link between xenoestrogens and breast cancer that the molecular methods to assess this link are limited and Western populations might be ubiquitously exposed to xenoestrogens which makes studies inconclusive. Hence, the need for looking at xenoestrogen-breast cancer association in new populations with differential exposures and development of new molecular methods for this purpose cannot be sufficiently overemphasized. That apart, these hypotheses in effect connect more closely the links between global differences in incidence of breast cancer, xenoestrogens, hormone receptor status of breast cancer and stem cells. The way in which the predictions of these hypotheses could be proven are not difficult and would add to the evidence which we seek in further defining the etiology of breast cancer. We must bear in mind that xenoestrogens are a preventable cause of breast cancer and this association between xenoestrogens and breast cancer if confirmed should lead us to policies that ban or regulate the use of xenoestrogens. Further research into mammary stem cells can result in better treatment and intervention at the appropriate time in the lifetime of a woman to reduce breast cancer incidence. In addition, monitoring efforts can be implemented that test all new manufactured chemicals for their hormonal effects and related consequent impacts on breast cancer incidence.

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