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Review

Breast cancer: Lesser-known facets and hypotheses

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ABSTRACT

Breast cancer is the most common cancer in females. The deteriorating environment, and lifestyle flaws are raising the frequency of this cancer. Existing therapies are not universally-effective, and they cause side effects, relapses, and high mortality rate. Alternative medications may be milder, but are less effective or are inadequate for a complex disease like the breast cancer. So, it requires the understanding that drugs are not the solution of this cancer, but prevention is the sustainable solution.

In the past decades, an enormous quantum of insights on this disease has been obtained. A lifestyle based on the template of estrogenic compounds and, the resultant endocrine disruption, and acidosis, is elevating aromatase level, promoting the deleterious forms of estrogen, and inducing epithelial proliferation. This review provids a holistic account of breast cancer as a inflammatory endocrinopathy, and how it can be curbed by discipline, and awareness.

1. Introduction

Cancer is an age-old disease that is associated with fear for its pain, unpredictable course of progress, inefficacy of existing therapeutics, serious side effects, and premature mortality. Earlier, cancer was more common in the industrialized regions of the world. Now, it has crossed the boundaries, and has gripped every geographical region, every economic stratum. Of all forms of cancer, breast cancer is a dominant cause of female morbidity and mortality. Its heterogeneity, variable subtypes, and different response to hormone (estrogen receptor positive (ERα+) as well estrogen receptor negative (ERα-)) make its therapy complicated, often futile [1].

A report says that breast cancer affects 1 out of 8 women in the USA, which is some grim statistics [2]. Understanding of cancer has undergone enormous shift, from the earlier perception of its as being a divine anathema, to the modern perception as the resultant of inflammations. Any part of the body can turn cancerous - neural (brain), respiratory (lungs), reproductive (breast, ovary, uterus, cervix, prostate gland, testis), urinary (kidney), digestive (mouth, esophagus, liver, pancreas, colon), vascular (blood, skin) among, others. Depending on the functional role of the organ, or the system, cancer can be easy to treat, or vicious.

Among all forms cancers, breast cancer is the most common cancer in females. It is heterogeneous, polygenic, and occurs in multiple subtypes such as luminal A, luminal B, HER2 (human epidermal growth factor receptor 2) overexpressing, normal-like and basal-like [3]. Some of the breast cancers are estrogen receptor positive (ERα+), while some are estrogen receptor negative (ERα-). This diversity of tumor types, and the signaling pathways renders therapies unpredictable [3].

Glands or lymph nodes are part of the lymphatic system, forming a reticulum throughout the body, tasked with the safety of human health from exogenous and endogenous threats. They constantly act as a radar to monitor the stressors. Breasts are made of adipose tissues intervened with lymphatic vessels, the mammary glands. Breasts have basement membranes, composed of laminin and collagen, which are required for duct morphogenesis.

Several paracrine growth factors such as epidermal growth factor (EGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and amphiregulin are involved in breast development. These growth factors are mediators of sex hormones and, growth hormone (GH) and insulin-like growth factor 1 (IGF-1). At puberty, the levels of GH and IGF-1 are at their highest, which give cues to secrete estrogen in high amounts. Mammary gland is an exocrine apocrine gland, also considered as modified sweat or sebaceous gland, that produces milk after parturition. Breast milk is essential for the healthy growth of infants. The mammary gland responds to estrogen, as well as above-mentioned growth factors, and changes breast tissue architecture during the prepubertal, puberty, reproductive age, pregnancy, lactating, and postmenopausal stage of a female [4]. During puberty, estrogen directs ductal system generation (branching morphogenesis), and stromal and fat tissue development [4]. During pregnancy, progesterone and prolactin lead to lobuloalveolar development in anticipation of lactation. Both estrogen and progesterone are controlled by the anterior pituitary lactogenic hormone prolactin [5].

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Both of these steroid hormones coordinate to maintain pregnancy, but progesterone protects against the deleterious action of estrogen. However, progesterone is likely to have its adverse effects, as infections and gestational diabetes instances are higher during pregnancy. Fluctuating estrogen level leads to the modification of breast tissues, rendering the organs vulnerable to inflammation. In fact, other glands such as hypothalamus, pituitary gland, pineal body, thyroid gland, parathyroid gland, adrenal glands, reproductive glands (ovaries and testes), pancreas, and prostate gland, are prone to cancer, when encountering stress for long enough.

Breast cancer is one disorder of breast tissues and mammary gland, as other structural anomalies can occur. The pathologies of breast cancer can be better understood by having a knowledge of other breast conditions. Gynecomastia is the proliferation of breast glandular tissues in the males [6]. High level of eexogenous or endogenous estrogen, GH and IGF-1 leads to the hyperplasia. Excess aromatase level causes prepubertal gynecomastia in males, and breast hypertrophy in females [7]. Increasingly, dangerous chemicals are being discovered in mothers' milk, due to intentional chemical (cosmetics, pharmaceutical, alcohol) usage, and accidental exposure (pollutants as heavy metals and volatile organic compounds) [8]. This review discusses the causes, mechanisms, therapies of breast cancer, and discusses hypothesizes why the instances of this pathology are rising and how they can be mitigated.

2. Triggers of breast cancer

Human life span has increased, but health issues are emerging due to the aging. Further, to keep up with the fast lifestyles, stress level had increased, begetting an assortment of physical and mental health problems. To counter these problems, several drugs are being used. In fact, the reliance on drugs has soared in unprecedented manner. The drugs might be resolving the health issue, but they are creating other problems. A list of medications has been presented in Table 1. From the information in the table, it can be inferred that a therapeutic intervention relies on the manipulation of hormones, so, it has consequences for estrogen level, and thus the risk of breast cancer.

Hormonal contraceptives increase aromatase induction in the body [9]. These external estrogens might be elevating breast and ovary cancer risk. Serum sex-hormone-binding globulins regulate circulating steroid level, so, decline in their level increases steroid level in females [10], which might be elevating breast cancer risks.

Apart from the drugs, other lifestyle habits are raising the risks of breast cancer, some of such factors have been listed in Table 2. Such endocrine-disrupting agents include substance abuse, dietary components, and additives, toiletries, household cleaning agents, physical recontouring for aesthetic enhancement *etc*. Direct connection might not be easy to show in some cases, but one thing leads to another issue, in a complex cascade of metabolic pathways, causing the problem.

Alcohol consumption raises the risk of breast cancer, apart from an array of other pathologies resultant of the beverage intake [11,12]. Processed foods cause acidosis [13], which activates inflammasomes [14], and result in aberrant enzyme activity. Paleo food, being less acidogenic, might prevent acidosis and retain normal physiological pH, had been reviewed [15].

Table 1
Medications that can influence hormones to cause breast cancer.

Medication class	Drug names
Aromatase inhibitors	Testolactone and anastrozole
Cardiac and antihypertensive/ calcium channel blockers/ACE inhibitors	Spironolactone, digitalis, digoxin, verapamil, nifedipine, diltiazem, captopril, enalapril, heparin
Infertility/miscarriage/synthetic estrogens drugs	Clomiphene, diethylstilbestrol
Infectious diseases drugs	Isoniazid, metronidazole
Acid reflux drugs	Cimetidine
Antidepressants	Diazepam
Chemotherapeutic drugs/ alkylating agents	Methotrexate, bicalutamide
Hormonal contraceptives, aphrodisiacs	Viagra

Table 2
Lifestyle factors that can influence hormones to cause breast cancer.

Estrogenic substances	Examples
Substance abuse	Alcohol, marijuana, heroin, cannabis, methadone, amphetamines
Toiletries such as hair dye, deodorant, sunscreen	Parabens, phthalates, nitro musks, benzophenones
Household cleaning agents	Floor mop, laundry detergent
Body manipulation	Tattoo, breast implant, Botox *etc*.
Diet	Phytoestrogens
Food additives	Synthetic color, preservatives
Pesticides	Glyphosates (Roundup)
Vehicle exhausts	*Heterocyclic amines, lead*

Indoor environment contains a large number of endocrine-disrupting chemicals such as plasticizers, emulsifiers, detergent metabolite, adhesive, fragrance, disinfectant, flame retardants, and pesticides. Bisphenol A (BPA), polychlorinated biphenyls (PCBs), polybrominated diphenyl ether (PBDE), triclosan *etc*. are estrogenic [16,17].

The link between haircare product and breast cancer risk has been proven [18]. Fragrance compounds used in the form of perfume, deodorant, air fresheners, dryer sheets *etc*. contain parabens, phthalates, nitro musks, and benzophenones, which penetrate blood stream through dermal contact, or inhalation, resulting in the disruption of endocrine homeostasis, inducing tumorigenesis [19,20]. Carcinogenic potential of fragrance compounds have been reviewed [21]. Toxic volatile organic compounds (VOCs) such as limonene, α- and β-pinene, ethanol, acetone *etc*. in personal care products are hormone disruptors as well [22]. Cosmetic products like deodorant, sunscreens, nail polish, lipstick, and eye shadow contribute to endocrine imbalance and inflammation. Ultraviolet (UV) filters in sunscreens are hazardous. A survey of 70 cosmetic products showed the presence of estradiol, estrone, estriol, and progesterone in them [23].

The list of products the modern females likely to be using is exhausting – hair dye, tanner, skin tightener, facial hair remover, acne controller, anti-aging product, among a large repertoire of other chemicals. Botox injection, to silicone implants, and physical modifications have increased in an unforeseen manner. Together, these chemicals create a 'ticking time bomb' situation for the vulnerable females. Vulnerability is the propensity to undergo immune activation faster than others, for which females of certain genotype and phenotype are more prone to.

Increasingly, air, soil and water are getting polluted. The inhalation, ingestion, and dermal contact of these pollutants are agitating hormones and activating the immune system. The common genotoxic chemicals include vehicle exhausts, industrial effluents, particulate matters, fire retardants, among others. In the last three decades chemical pesticide usage has risen in an unprecedented manner. Some pesticides like glyphosate contaminate water sources [24–26], which ultimately make way into human system. Fig. 1 shows a list of estrogen mimics that are encountered in day-to-day life.

Some occupations expose individuals to a higher risk of breast cancer. Beauticians, nail technicians, hair dressers are more prone to breast cancer, as the cosmetics are inhaled as aerosol. People in show business are often caked with cosmetics, so the instances of breast cancer are often higher in them. Those living in close proximity to chemical-sprayed agricultural fields are more prone to breast cancer has been proven [27].

A recent study has shown that infections with Epstein-Barr virus (EBV), Human papillomavirus (HPV), and mouse mammary tumor virus