The Role of Xenoestrogens in Breast Cancer Development and Progression

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Abstract

Breast cancer is the fifth most common cause of cancer death in the world and the second most common fatal cancer in women. Breast cancer is an invasive malignancy among women worldwide and constitutes a complex and heterogeneous disease. Xenoestrogens, a class of endocrine-disrupting chemicals (EDCs), are increasingly recognized for their role in breast cancer development and progression. These are found in industrial chemicals, pesticides, personal care products, and dietary sources, which mimic or interfere with natural estrogens' actions by binding to estrogen receptors. This chapter explores the mechanisms through which xenoestrogens contribute to breast cancer, including their activation of estrogen receptor-mediated pathways, disruption of genomic and non-genomic signalling, induction of oxidative stress, and epigenetic alterations. Epidemiological and experimental evidence highlights a strong correlation between xenoestrogen exposure and increased breast cancer risk. Furthermore, the chapter discusses the sources and pathways of xenoestrogen exposure, emphasizing the need for regulatory policies, public awareness, and lifestyle modifications to reduce risks. Advances in biomarkers and detoxification strategies offer hope for mitigating the impact of these chemicals. The chapter concludes with future research directions, focusing on molecular mechanisms, long-term exposure studies, and targeted interventions. Understanding and addressing the role of xenoestrogens is crucial for improving breast cancer prevention and treatment outcomes, as well as for safeguarding public health.

Keywords: Breast cancer, Xenoestrogens, Oxidative stress, Biomarkers, Endocrine disrupters

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Introduction

1.1 Overview of Breast Cancer

According to the WHO, breast cancer has a significant public health burden, with nearly 2.3 million patients diagnosed globally in 2020. Over the years, it has become quite apparent that breast tissue, conditioned by genetic, environmental, and hormonal factors, is the site of uncontrolled cellular proliferation. The increasing age, family history, hormonal imbalance together with lifestyle factors like alcohol consumption, obesity, and lack of physical activity are the risk factors associated with breast cancer (Pinto et al., 2023). Being exposed to environmental pollutants, especially chemicals that mimic hormones is now becoming a risk factor of breast cancer. There is now an increasing survival rate as a result of the innovations made in advanced technologies; however, challenges persist in accessing health services, and genetic compositional and environmental problems (Park et al., 2007). This underlines the fact that all the variables including the assessment of environmental factors like xenoestrogens need to be revisited (Safe et al., 2022).

1.2 Understanding Xenoestrogens

Xenoestrogens are endocrine-disrupting chemicals (EDCs) that mimic or interfere with normal estrogen hormones in the body. Currently, these synthetic substances have been detected in a number of industrial chemicals, insecticides, polymers, and personal products (Gore et al., 2015). Xenoestrogens may bind to estrogen receptors mimicking the physiological estrogen oestradiol and thereby stimulate several signal transduction events involved in cell growth, differentiation and survival. This disrupted hormonal activity creates a suitably permissive context for breast carcinogenesis. Some of the xenoestrogens are relatively refractive to metabolism and are thus existent in human tissues for a long time, which makes their exposure to be more prolonged (Rodgers et al., 2018). This is because their effectiveness at low levels of consumption and their ubiquity in modern lives boost their impact. Examples of xenoestrogens include bisphenol A (BPA) found in material that goes into plastics, phthalates in other individual care products, and pesticides, especially DDT. These chemicals have been detected in humans in various biological fluids including blood, urine, and breast tissue (Starek-´Swiechowicz et al., 2017).

1.3. Importance of Studying Xenoestrogens

The study of xenoestrogens is important given their non-specific impacts and involvement in the development of breast cancer. Several researches have established a link between increased breast cancer risks and xenoestrogen exposure. More recent studies have elucidated

precisely how these substances disrupt the normal activity of cells and promote tumor formation and metastasis (Bergman et al., 2013; Feng et al., 2016). The effects of xenoestrogens on human health are wide-ranging because they raise the rates of breast cancer and other estrogen-related diseases, including endometriosis and infertility (Karakus et al., 2015). Furthermore, pregnant women and young persons and those who are likely to have genetic predispositions are likely to come across with higher risks. Reduction of xenoestrogen exposure requires regulation, sensitization campaigns and targeted research on how best to solve the problems of prevention and risk management. Classification of various types of xenoestrogens is given in table 1. Understanding the interplay between genetics, environment, and hormonal influence would help in developing the best approach to mitigate breast cancer (Ahern et al., 2019).

Table 1: Classification of Various Types of Xenoestrogens, including Phytoestrogens, Pesticides, Phenols, Mycoestrogens, and Metalloestrogens.

Xenoestrogens	Phytoestrogens	Isoflavones	(Anderson et al., 2021; Schluter et al., 2024).
		Stilenes	
		Equol	
	Pesticides	DDT	
	Phenols	Bisphenol A	
	Mycoestrogens	Zearalenone	
		Ochratoxin A	
	Metalloestrogens	Mercury	
		Cadmium	
		Chromium	
		Zinc	
		Nickel	
		Copper	
		Lead	
		Aluminium	
		Cobalt	

2. Mechanisms of Xenoestrogens in Breast Cancer Development

2.1 Estrogen Receptor Activation by Xenoestrogens

Xenoestrogens disrupt biological processes by interacting with ER-α and ER-β receptors, therefore, mimicking the estradiol hormone. This interaction disrupts the hormonal balance in cells to trigger metastatic docking and activates estrogen-related pathways. Xenoestrogens are different from normal estrogens as they cause receptor activation for a long time provoking excessive cell division and immune to cell death (Brody & Rudel, 2003). These account for the uncontrolled division of cells exhibited in breast tissues thus laying a background to tumorigenesis. Since different xenoestrogens have different affinity values for the estrogen receptors, it is likely that certain xenoestrogens are different from normal estrogens as they cause prolonged receptor activation leading to excessive cell division and cellular death (Gore et al., 2015) In these systems, xenoestrogens are proposed to act synergistically with endogenous estrogens, enhancing hormonal signals that initiate cell replication. This interaction may expedite the advancement of estrogen-dependent cancers in individuals with genetic or environmental susceptibilities. Xenoestrogen including BPA is capable of binding to nuclear estrogen receptors as shown in Figure 1. Furthermore, these compounds have demonstrated the ability to modify the cellular environment, facilitating processes like angiogenesis and establishing conditions conducive to tumor development, as indicated in the research conducted by Jiang et al. (2020).

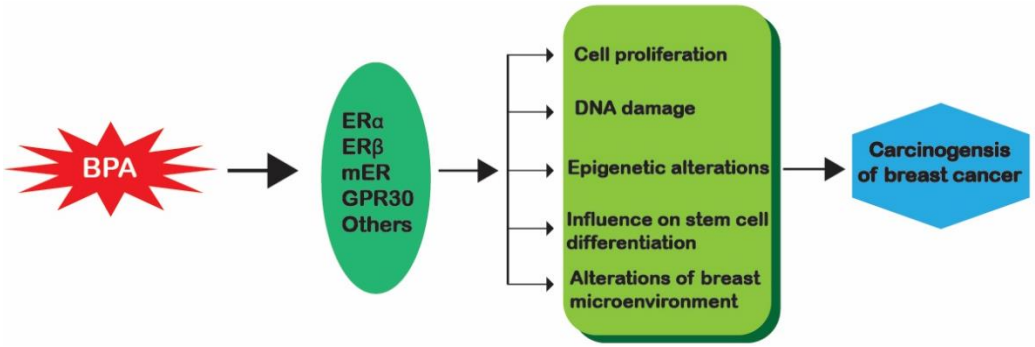

Fig. 1: Xenoestrogen BPA can interact with nuclear estrogen receptors (ERs), cytoplasmic ERs, membrane-bound ERs and GPR30 receptors, inducing mammary epithelial cell proliferation through genomic and non-genomic signaling pathways.

2.2 Genomic and Non-Genomic Pathways

The variety of action of xenoestrogens both in the genomic and non-genomic ways indicates the complex involvement of xenoestrogens in the breast cancer progression. Xenoestrogens affect the expression of genes that are regulated by estrogen in the genomic ways mainly by binding to the estrogen receptor that binds to DNA at estrogen response elements (EREs) This transcriptional activity alters the genes that control DNA synthesis, cell cycles, and anti-apoptotic genes as well. There is the rise of cyclin D1 which is on the cell cycle which means that xenoestrogens cause the cells to proliferate fast (De Coster et al., 2012).

Xenoestrogens quickly trigger cytoplasmic signaling cascades through non-gene activation without entering the nucleus. Such pathways are MAPK and phosphatidylinositol 3-kinase/ Akt (PI3K/Akt) pathways that regulate cell survival, motility, and invasiveness. The activation of

these pathways enhances metastatic potential since xenoestrogens facilitate epithelial-to-mesenchymal transition (EMT), a critical mechanism in cancer spread. The interaction between genomic and non-genomic pathways enhances the carcinogenic potential of xenoestrogens (Darbre, 2008). Schematic diagram of XEs exposure that may lead to cancer is depicted in Figure 2.

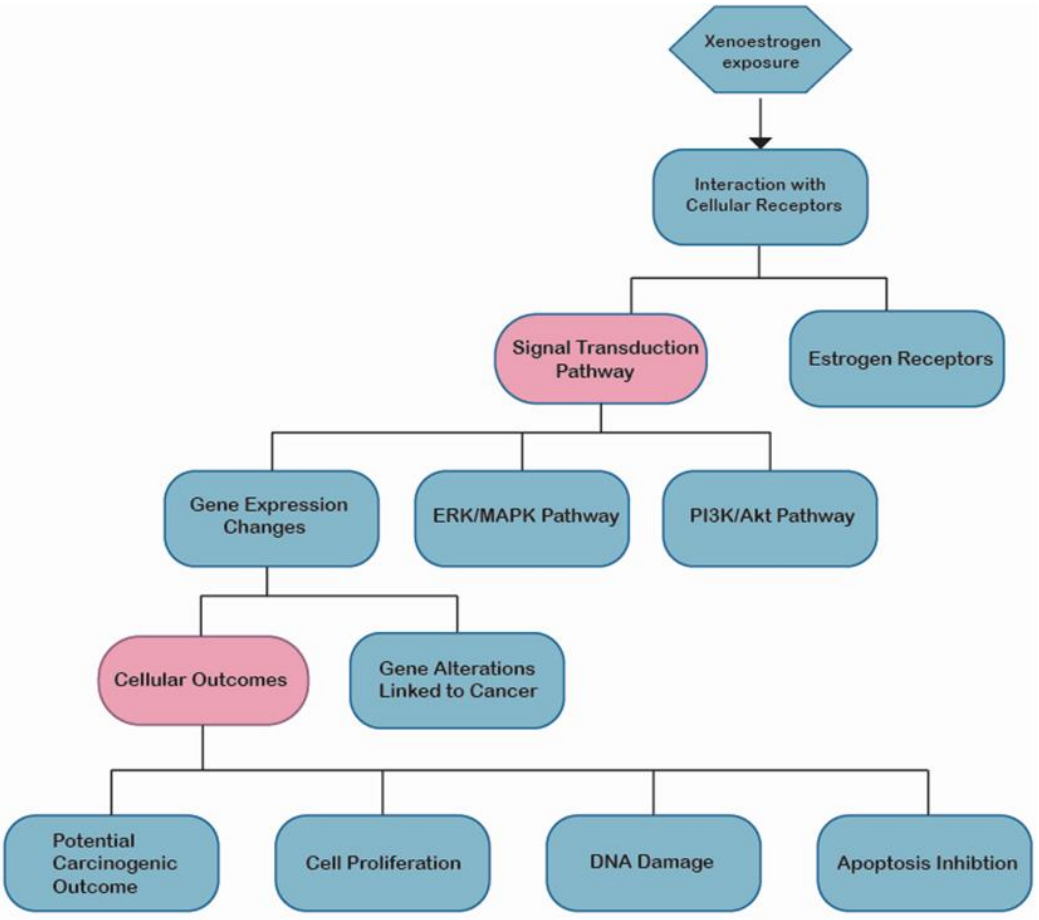

Fig. 2: The molecular pathway by which XEs exposure may lead to carcinogenesis.

2.3 Epigenetic Modifications Induced by Xenoestrogens

Epigenetic alterations provide a significant mechanism of xenoestrogens in breast cancer progression. In contrast to genetic mutations, epigenetic modifications are reversible changes in gene expression that do not include alterations to the DNA sequence. Xenoestrogens are associated with the induction of DNA methylation, histone changes, and non-coding RNA expression, all of which lead to modified cellular phenotypes (Feng et al., 2016).

Research has shown hypermethylation of tumor suppressor genes, including BRCA1 and p53, due to xenoestrogen exposure, resulting in their silencing and the consequent loss of tumor-suppressive capabilities. Additionally, a decrease of DNA methylation of tumor-promoting genes may lead to their over-expression, which in conjunction with up-regulation of oncogenes pushes the balance of the cell toward tumor formation (Diamanti-Kandarakis et al., 2009). Histone acetylation and methylation regulation marks are also affected in similar manners: the overall shape of chromatin is changed and nucleosomal regions become opened to various transcription factors. Moreover, xenoestrogens affect the expression of microRNAs (miRNAs), which are tiny non-coding RNAs that modulate gene expression after transcription. Alterations in miRNA regulation linked to cell proliferation, differentiation, and apoptosis have been noted in breast cancer models exposed to xenoestrogens. These epigenetic alterations not only facilitate carcinogenesis but also enhance therapeutic resistance, complicating treatment results (De Coster et al., 2012). BPA affects the breast microenvironment and facilitates breast cancer development by altering the surroundings of mammary epithelial cells (Figure 3).

2.4 Oxidative Stress and DNA Damage

Oxidative stress is a disparity between the reactive oxygen species (ROS) generation and antioxidant enzyme defences and is a defining feature of xenoestrogen exposure. Xenoestrogens induce ROS by many mechanisms, such as mitochondrial impairment and the activation of NADPH oxidases (Feng et al., 2016). Increased ROS levels lead to oxidative degradation of biological macromolecules, such as lipids, proteins, and DNA. ROS induce DNA damage by base alterations, strand breakage, and crosslinking, undermining genomic integrity and facilitating mutagenesis (Kortenkamp, 2007). Chronic oxidative stress stimulates signalling pathways, including nuclear factor kappa B (NF-κB) and hypoxia-inducible factor 1-alpha (HIF-1α), facilitating cell survival, angiogenesis, and immunological evasion. Diagrammatic representation of potential pathways through which BPA drives mammary carcinogenesis is given in Figure 4. These pro-survival mechanisms facilitate the persistence of cancer cells in the adverse tumor microenvironment (Gore et al., 2015).

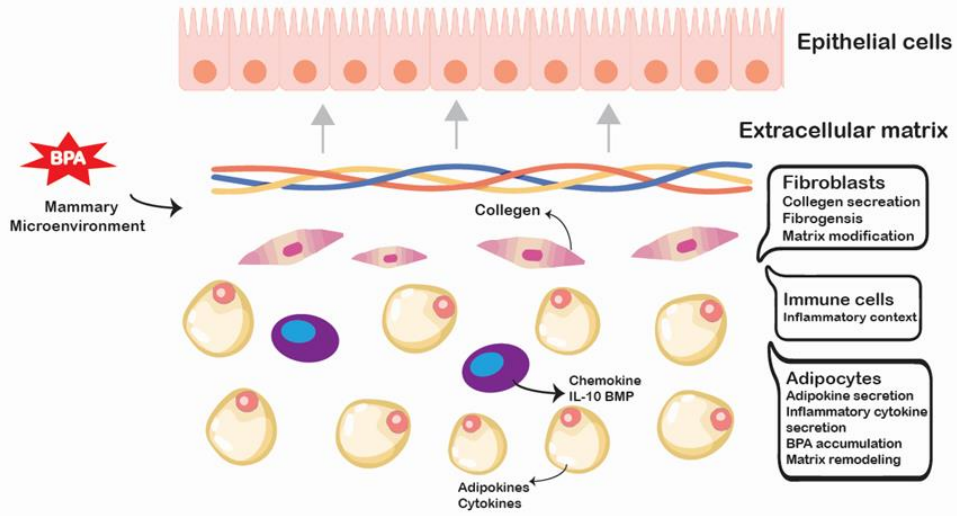

Fig. 3: A schematic representation illustrating the impact of BPA on the breast microenvironment. BPA promotes the development of breast cancer by influencing the microenvironment around mammary epithelial cells. BPA may negatively affect many cell types in the gland, including fibroblasts, adipocytes, and immune cells, therefore altering the release of soluble factors, components, and organization of the extracellular matrix, and the local immunological environment. These abnormalities may result in persistent inflammation, disruption of the balance of tissues, and neoplastic alterations in mammary epithelial cells.

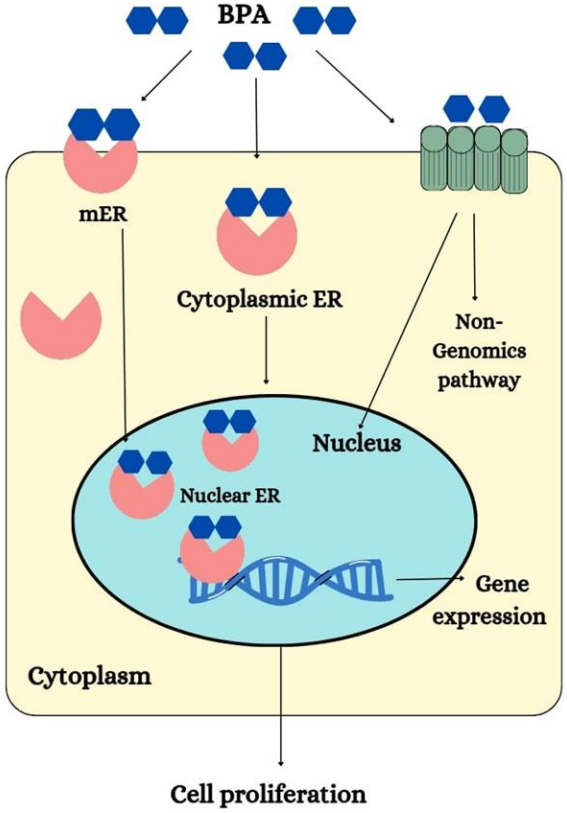

Fig. 4: Schematic overview of possible pathways by which BPA promotes mammary carcinogenesis.

Furthermore, oxidative stress generated by xenoestrogens has been associated with activating redox-sensitive transcription factors that govern the expression of genes related to detoxification, inflammation, and cell proliferation (Anderson et al., 2021). The interaction between oxidative stress and processes including estrogen receptor signalling and epigenetic alterations creates a detrimental loop that sustains tumor development. Consequently, xenoestrogens trigger breast cancer development through a variety of complicated pathways of estrogen receptor binding, modulation of genomic and non-genomic signaling, epigenetic changes, and generation of oxidative stress. Understanding these pathways is important for developing specific treatment strategies that will negate the impact of xenoestrogens on breast cancer risk (Gachowska et al., 2024).

3. Sources of Xenoestrogens and Exposure Pathways

3.1 Environmental Sources

A major route of xenoestrogen intake is through contaminated environments, the biggest culprits being industries. BPA, Phthalates, and polychlorinated biphenyls (PCBs) are the major xenoestrogens that remain persistent in ecosystems due to their chemical stability (Wang et al., 2021).

a) **BPA:** BPA is widely used today in the production of polycarbonate plastics and epoxy resins, and widely used in products like food containers, water bottles, and even in thermally printed paper products like receipts. BPA is ingested into the environment through manufacturing processes and unproper disposal, hence contaminating soil, water, and air. It has been linked with estrogenic activity and cellular changeover that is associated with breast cancer (Gore et al., 2015).

b) **Phthalates:** These compounds function as plasticizers, enhancing the flexibility of plastics used in items such as toys, medical apparatus, and food packaging. Phthalates are emitted throughout the product lifespan, infiltrating the environment and ultimately bioaccumulating in people by ingestion, inhalation, and skin absorption. Prolonged exposure has been linked to hormone dysregulation and cancer development (Sun et al., 2019).

c) Polychlorinated Biphenyls (PCBs): Despite being prohibited in several nations, PCBs persist as environmental pollutants owing to their prior use in electrical apparatus and industrial applications. PCBs bioaccumulate in the food chain and demonstrate oestrogenic and anti-estrogenic properties, prompting worries about their involvement in breast cancer advancement. These environmental sources highlight the need for rigorous restrictions and novel waste management measures to reduce human exposure to xenoestrogens (Anderson et al., 2021).

3.2 Dietary Sources

Diet is also a major route for xenoestrogen exposure since diverse pollutants in food items and natural chemicals in certain plants contribute to the xenoestrogenic load (Karakus et al., 2015). Some of these xenoestrogens may mimic estrogen due to similarity in structure

since they bind estrogen receptors and hence influence the hormone-controlled processes (Thayer et al., 2016). While the intake of phytoestrogens boosts the health potential it can increase the propensity of breast cancer given its oestrogenic attributes, particularly in women with hormonal disorders or family history of the disease. Consuming such raw food intensifies the risk of coming into contact with the abovementioned adverse compounds especially where proper washing or peeling is not done. To manage the challenges arising from dietary sources of xenoestrogens proper food safety measures have to be adopted (Jiang et al., 2020). Measures on a stricter regime on certain food packaging may also control the leaching of certain undesirable substances; the existence of control on oestrogenic pesticides may also be reduced with the promotion of organic agriculture (Anderson et al., 2021). Such awareness and preventative measures might help the stakeholders to try and reduce the health risks that have been associated with xenoestrogens and consequently, the safety of the foods that are consumed is improved (Thayer et al., 2016).

3.3 Personal Care and Household Products

The intake of xenoestrogens extends beyond food and drinking water; regular use of cosmetics, detergents, shampoos, and other personal care products constitutes a considerable additional source of exposure. Parabens and synthetic fragrances are common contributors to xenoestrogen ingestion through habitual use (Feng et al., 2016).

Parabens: These preservatives, used in cosmetics, lotions, and shampoos, exhibit estrogen-mimicking characteristics. Research suggests that parabens may infiltrate the epidermis and accumulate in breast tissue, possibly affecting the development of breast cancer (Darbre, 2008).

Synthetic scents: Present in perfumes, deodorants, and air fresheners, synthetic scents often contain phthalates, which enhance their durability and aroma retention. Extended exposure by inhalation or skin absorption increases the likelihood of hormonal disturbances (Wang et al., 2021). Household cleaning products may include oestrogenic chemicals, such as nonylphenol, which are detrimental to human health and contribute to environmental pollution. Minimizing dependence on synthetic personal hygiene and home items while advocating for natural alternatives is crucial for decreasing xenoestrogen exposure (Gachowska et al., 2024)

4. Epidemiological Evidence Linking Xenoestrogens to Breast Cancer

Population-based research over the years has caused considerable evidence to support the hypothesis that exposure to xenoestrogens leads to breast cancer and established the potential impact that these environmental chemicals play in the development of the disease (Gore et al., 2015). Due to its advantages, biomonitoring data from population studies have been used to estimate the levels of circulating xenoestrogens including BPA and phthalates (Diamanti-Kandarakis et al., 2009). Such studies help identify the carcinogenicity of xenoestrogens by relating the levels of these chemicals to occurrences of breast cancer (Feng et al., 2016). Several studies have established a relationship between increased BPA levels and increased risk of breast cancer. BPA is a common industrial chemical that exists in human blood and urine samples. It has been observed a positive association between BPA exposure and that of ER+ breast cancer cells (De Coster et al., 2012). Their finding shows that BPA is capable of mimicking estrogen which is an important hormone in the progression of breast cancer most especially the hormone-sensitive type (Kortenkamp, 2007). Apart from pesticides, xenoestrogenic agents also contained in plastics and personal care products such as phthalates are linked to breast cancer (Karakus et al., 2015). Adding geographical and occupational variables helps to explain the relationship between xenoestrogens and breast cancer. Industries that are located in industrialized areas experiencing high levels of pollution and other environmental xenoestrogen enhance breast cancer incidence rates in women. Similarly, in industries and agriculture sectors exposed to chemicals, employees are exposed to higher risks and complications associated with the chemicals used (Park et al., 2007; Yu et al., 2024).

5. Strategies for Prevention and Mitigation

5.1 Regulatory Framework and Directives

Effective regulation should encompass rules and recommendations designed to minimize exposure to xenoestrogens and mitigate their associated risks. Organizations like the European Chemicals Agency (ECHA) and the U.S. Environmental Protection Agency (EPA) have established regulations concerning the production and utilization of hazardous xenoestrogens, including BPA and specific phthalates (Park et al., 2007). These strategies are envisaged to reduce pollution of the environment and man's vulnerability to its impacts and mark a giant step ahead in the protection of man and his environment (Starek-´Swiechowicz et al., 2017). However, differences in the potential regulatory standards cause complications in effective prevention strategies (Donovan et al., 2018). There is a need to harmonize policies all over the globe in order to equally protect people against xenoestrogens because the imposition of different rules could slow down progress (Pinto et al., 2023). However, enforcement deficiencies have been observed to persist hailing from lack of resources, and inconsistent objectives of agencies (Bergman et al., 2013). There is enormous need to develop a comprehensive approach with no gaps and inconsistencies in addressing the global challenges associated with exposure to xenoestrogen (Avila-Galvez et al., 2020).

5.2 Progress in Screening and Detoxification

Xenoestrogens can potentially be reduced through scientific advancements (Guneydas et al., 2022). Identifying exposure early, developing novel approaches, and exploring potential detoxification mechanisms are essential areas of focus in mitigating their impact (Wang et al., 2021). Regarding increasing early detection, biomarkers have become universally important in their creation (Gupta et al., 2021). Therefore, the reliable biomarkers that indicate the exposure to the xenoestrogen should be generated and this makes it easier to respond immediately (Starek-´Swiechowicz et al., 2017). The current research is focused on improving these methods for more general application to clinical settings for providing responsible and precise measures that predict the exposure levels and health risks (Schluter et al., 2024). Dietary intervention for enhancing the body detoxification ability is being studied in depth (Rodgers et al., 2018). Consumption of foods with antioxidant properties, for instance, cruciferous vegetables also; supplements like probiotics, have been noted to have capability to improve the human body's ability to metabolize and eliminate xenoestrogens (Farhan et al., 2022). These dietary suggestions might greatly decrease overall body xenoestrogen

burden, particularly in targeted subgroups (Sikder et al., 2024).

New technologies are appearing in the prevention of environmental exposure to xenoestrogens. Purification systems that are supposed to filter water and effectively improve air quality should be understood as developing technologies that can significantly decrease exposure (Yu et al., 2024). By the implementation these technologies coupled with very strict and sensitive regulatory approaches could play an important role in addressing the issues of xenoestrogens in public health (Ahern et al., 2019). The scientific world is focusing a lot of effort to overcome the challenges posed by xenoestrogens through the identification of biomarkers, nutrition, and utilization of new technologies (Rodgers et al., 2018). These initiatives suggest that the achievement of better health and a clean, safe environment requires an intersectoral approach (Schluter et al., 2024).

6. Prospects for Further Research

6.1 Establishing Molecular Mechanisms

Continuing investigation should therefore be directed at determining how these xenoestrogens bring about alterations in the progression of breast cancer, at the molecular level. Some of these chemicals are man-made or occur naturally and bind to estrogen and/or estrogen receptors that can either initiate or progress cancer processes (Ruiz et al., 2021). Such techniques as CRISPR-Cas9 gene modification and 'multi-omics' approaches genomics, proteomics, and metabolomics offer exceptional chances of understanding these processes. CRISPR is used to edit genes associated with estrogen signaling, thereby increasing the specificity of the studies on causal relationships. Therefore, improved approaches for early diagnosis of xenoestrogens are established by using multi-omics strategies to analyze modulatory effects on complex biological systems (Boszkiewicz et al., 2023). Understanding the biochemical nature of the interactions between xenoestrogens and breast cancer requires the development of viable cell cultures and animal models (Ruiz et al., 2021; Miret et al., 2023). Higher-end 3D organoid cultures and humanized animals could mimic human breast tissue environment and setting to reveal on the effects of xenoestrogens on cell division, cell death, and migration (Hager et al., 2022). Furthermore, possible changes, such as DNA methylation and histone acetylation agonist to xenoestrogens may contribute to likely mechanisms for passing on the risk of developing cancer to the next generations (Kwon, 2022).

6.2 Advancement of Targeted Therapies

New treatment strategies are thus required to reduce the effects of xenoestrogens. One approach may be the development of selective drugs that block the binding of estrogen to its receptor or molecules which interfere with the further signaling pathways. Based on the assessed data, current methodologies include Selective estrogen receptor modulators (SERMs) and Selective estrogen receptor degraders (SERDs) that can be developed for improved specificity targeting xenoestrogen-related pathways (du Plessis et al., 2023). For instance, SERMs can be refined to afford the possibility of blocking the xenoestrogen-induced signaling as well as retaining the benefits of estrogen signaling. A potential strategy is small molecular inhibitors of ER co-regulatory proteins (Sawicka et al., 2024). Cancer vaccines, which target xenoestrogen-modified proteins that can be targeted by immunotherapy methods, may have substantial potential. These medicines might represent a novel way to treat breast cancer by enhancing the immune system's ability to reject cancer cells that are transformed by xenoestrogens (Maharjan et al 2021). Conducted with conventional chemotherapeutics, administration of the targeted treatments may substantially enhance effectiveness, especially in the case of first- or second-line treatment failures in advanced or chemo-resistant diseases (Del Favero et al., 2024). For instance, nanoparticles based targeted delivery of chemotherapeutic drugs is a groundbreaking approach which enhances the drug efficieny, half-life, retainability as well as stability (Salar et al., 2024). Therefore, the incorportation of new techniques with traditional therapies can be beneficial as well as effective.

Conclusion

Xenoestrogens, found in industrial products, personal care items, food, and environmental pollutants, are linked to increased breast cancer risk. These endocrine-disrupting chemicals interfere with estrogen signaling, promote oxidative stress, and alter epigenetic patterns, creating conditions for tumor development and metastasis. Although evidence suggests a connection between xenoestrogen exposure and breast cancer, establishing direct causality is chal lenging due to the complex nature of exposure. Addressing this issue requires stronger regulations, public awareness, and lifestyle changes. Advances in biomarker studies and detoxification methods offer hope for early detection and prevention. Developing targeted therapies to counteract xenoestrogen effects could improve breast cancer outcomes. A comprehensive approach involving scientific research, policy action, and public engagement is essential to reduce xenoestrogen exposure and enhance breast cancer prevention and public health.

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