Review article

Exposure to selected environmental xenoestrogens and breast cancer – a review of recent studies

Izabela Domańska[1], Aleksandra Sagan[1], Monika Domagała[2], Weronika Duda[3], Emilia Majewska[4], Małgorzata Piśkiewicz[3], Joanna Wiewióra[5]

[1] Ludwik Rydygier Specialist Hospital in Krakow

[2] Military Clinical Hospital with Polyclinic SPZOZ in Cracow

[3] Provincial Complex Hospital in Kielce

[4] Dr. Tytus Chałubiński Specialist Hospital in Radom

[5] Provincial Hospital in Bielsko-Biała

ABSTRACT

Breast cancer is one of the most frequently diagnosed cancers in women worldwide and poses a significant challenge to modern medicine and public health. The increase in the incidence of this type of cancer is associated with various factors, including genetic, hormonal, lifestyle, and exposure to harmful environmental substances. In recent years, particular attention has been paid to xenoestrogens – synthetic chemical compounds present in the environment that mimic the action of natural estrogens and can disrupt the human hormonal system. Xenoestrogens are found in many everyday products, such as plastic packaging, cosmetics, detergents, and some pesticides. Scientists increasingly indicate a possible link between their action and an increased risk of breast cancer development. The mechanism of action of these substances is based on their ability to bind to estrogen receptors in the body's cells, which may promote uncontrolled cell division and the development of cancerous changes. This paper aims to present the mechanisms of action of selected environmental xenoestrogens, their sources in the human environment, and discuss current research on their potential impact on breast cancer risk.

Key words: breast cancer, bisphenol A, parabens, phthalates, endocrine-disrupting compounds

Correspondence:
Izabela Domańska, MD
Ludwik Rydygier Specialist Hospital in Krakow
31-826 Kraków, os. Złotej Jesieni 1
e-mail: izabeladomanska@gmail.com

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INTRODUCTION

Breast cancer is the most frequently diagnosed malignant tumor among women and the second leading cause of death in this group of patients, after lung cancer [1]. Despite many available treatment methods, it remains a significant health problem. To effectively prevent breast cancer, it is essential to know the risk factors, including exposure to estrogens – either endogenous or, as in the case of the selected endocrine-disrupting compounds (EDCs) described below [2, 3]. EDCs are "exogenous substances or mixtures that alter the functions of the hormonal system and consequently cause adverse health effects in an intact organism or its descendants" (definition by the World Health Organization, 2002) [4]. Xenoestrogens are among the EDCs, mimicking the action of estradiol and affecting the estrogen pathway [5]. The impact of xenoestrogens on breast cancer risk has been analyzed due to their carcinogenic effect on mammary gland epithelial cells. The aim of our work is to describe 3 xenoestrogens most commonly found in everyday products: bisphenol A, parabens, and phthalates, to determine whether and how they are related to breast cancer development [6–9].

ESTROGEN-DEPENDENT AND ESTROGEN RECEPTOR-DEPENDENT CARCINOGENESIS

Estrogens are female sex hormones, including estradiol (E2), estrone (E1), estriol (E3), and estetrol (E4). Before menopause, the dominant and most active endogenous sex hormone is E2, during pregnancy E4, and in postmenopausal women E1. Their synthesis occurs in the ovaries, adrenal cortex, and adipose tissue, originating from low-density cholesterol molecules, i.e. LDL. The development of the mammary gland, i.e. growth and cell proliferation, results from the binding of estrogens to estrogen receptors (ER) ERα and Erβ [10, 11]. Estradiol and its metabolites contribute to the formation of the cancerous process in breast epithelial cells. E2 and E1 are metabolized through 3 pathways catalyzed by cytochrome P450 enzymes and biotransformed into catecholoestrogens: 2-hydroxyestrone, 4-hydroxyestrone, 2-hydroxyestradiol, 4-hydroxyestradiol, 16α-hydroxyestrone, and estriol. Through further transformations, these compounds undergo methylation, forming 2-, 3-, and 4-methoxyestrogens, thus becoming resistant to further oxidation reactions.

Catecholoestrogens undergo redox processes, producing reactive oxygen species (ROS) that damage DNA. ROS initiate and promote oncogenesis and have mutagenic effects, damaging both DNA and mRNA. Further oxidative metabolism of catechols leads to the formation of quinones, particularly the harmful 3,4-quinone, forming adducts with adenine and guanine in DNA, leading to depurination and mutations [12, 13]. Estradiol can bind to the GPER1 membrane receptor or the nuclear receptors ERα or ERβ in the cytoplasm of breast epithelial cells. The classical estrogen signaling mechanism involves the binding of ERα–E2, resulting in complex translocation and binding to chromatin in estrogen response elements (ERE). This leads to the induction of activator protein-1 (AP-1), a transcription factor responsible for cell differentiation, proliferation, and apoptosis processes. Additionally, it can lead to the expression of IGF1, collagenase, IGF1 receptor, ovalbumin, and cyclin D1 genes [10].

PURPOSE OF THE STUDY

The purpose of this study is to review current research on the impact of selected xenoestrogens on breast cancer development, focusing on molecular mechanisms and epidemiological evidence supporting the link between xenoestrogens exposure and cancer risk.

MATERIALS AND METHODS

To find relevant studies, the PubMed database was searched using phrases such as "breast cancer and xenoestrogens", "BPA and breast cancer", "phthalates and breast cancer", "parabens and breast cancer", "DEHP breast cancer", "DBP breast cancer", and "xenoestrogens mammary gland". The article was prepared based on the latest publications in English.

BISPHENOL A

Bisphenol A (BPA) is one of the most widespread xenoestrogens found in many everyday items [14–16]. It is a synthetic organic compound from the phenol group, which, due to its structure, binds to ERs – both ERα and ERβ [17]. Besides its endocrine action (disrupting the binding of endogenous hormones to the above-mentioned receptors) [18], it also shows a link to breast, ovarian, and endometrial cancers, as well as to infertility, obesity, adverse neuropsychiatric effects, and asthma [19]. Humans are exposed to BPA through various routes due to its widespread presence, with the primary source being diet, specifically packaging: cans, containers, plastic boxes, etc. It tends to accumulate in tissues, and its presence has been detected in serum, urine, placenta, breast milk, and amniotic fluid [20]. However, it turned out that there is no link between BPA presence in serum and urine, and breast cancer incidence, as evidenced by 2 studies conducted in Spain [20] and the United States [21]. Salamanca-Fernández et al. identified 2 groups: one with breast or prostate cancer at recruitment, and the other, a suitably sized control group without such disease at the same time. It turned out that the geometric

mean BPA concentrations in samples taken from participants with diagnosed cancer were slightly higher than in participants from the second sub-cohort (1.12 ng/mL compared to 1.10 ng/mL) (p = 0.754). Statistical analysis did not show a significant link between BPA levels in serum and breast cancer incidence. Wu et al. considered the levels of BPA, triclosan, and parabens (also described later in our work) in urine collected before cancer diagnosis. The study group consisted of postmenopausal women of various ethnicities, with a mean age of 66.7 and 66.8 years in the breast cancer diagnosed and control groups, respectively. It turned out that BPA exposure is not associated with breast cancer. However, when it came to parabens, the result was surprising. Paraben exposure was inversely correlated with the risk of cancer. However, the study's conclusion did not indicate a link between parabens and breast cancer. In a mouse study [14], the impact of in utero BPA exposure on mammary gland stromal remodeling and its potential consequences, including breast cancer, was examined. Pregnant mice were given 25 µg/kg body weight of BPA. The effect of this treatment on the offspring's fibroblasts was analyzed at 12–14 weeks of age. Significant dysregulation in the transcription of genes related to carcinogenesis pathways, specifically the extracellular matrix composition, was demonstrated. The result was increased collagen deposition in the mammary gland of adults, lower extracellular matrix (ECM) permeability, and increased gland stiffness. Such changes favor tumor development and occur during the oncogenic transformation in human breast cancer [22–24]. In Verga et al. [19] study, the aim was to investigate the consequences of exposure to EDCs. The impact of BPA on the estrogen-dependent breast cancer cell line MCF-7 and mammary glands of 6-week-old mice was examined. An increased expression of enhancer of zeste homolog 2 (EZH2) was detected. EZH2 is a histone methyltransferase, and increased expression of this enzyme gene is detected in breast cancer. Concerning the impact of low doses of the described phthalates on the MCF-7 cell line, it was discovered that they increased viability. Exposure to one of the phthalates – di(2-ethylhexyl) phthalate (DEHP) on healthy human cells induced DNA damage, resulting in increased cell proliferation and tumor invasiveness.

In the in silico study by Warrier et al. [15], researchers investigated genes targeted by xenoestrogens, the effects of their expression following exposure to these substances, and their potential association with breast cancer development. The study examined various xenoestrogens, including BPA, as well as 4-tert-octylphenol (OP), nonylphenol (NP), and 2,2-bis(4-hydroxyphenyl)-1,1,1-trichloroethane (HPTE). A total of 25,521 genes were identified as having direct or indirect interactions with BPA, among which 68 were found to interact with at least 3 of the 4 studied xenoestrogens. Among various cancers, this gene set was most strongly associated with breast cancer. Additionally, a KEGG pathway (Kyoto Encyclopedia of Genes and Genomes) analysis revealed that these genes are implicated in carcinogenesis-related pathways, including chemical activation of carcinogenesis receptors, the mitogen-activated protein kinase (MAPK) signaling pathway, and the estrogen signaling pathway.

Genes whose expression increased upon exposure to all the studied xenoestrogens included ESR1, ESR2, MAPK1, MAPK3, PGR, TGFβ3, TNF, DDIT3, CYP19A1, CLU, FOS, HSD3B1, and BCL2 (tab. 1).

Table 1. Genes identified in the study and their relationship with breast cancer.

ESR1, ESR2	These genes encode the ERα and ERβ receptors, respectively. It is well-known that ERα is associated with the development of breast cancer [25].
MAPK1, MAPK2	Genes from the mitogen-activated protein kinase family. Dysfunctions in this signaling pathway are linked to tumorigenesis [26, 27].
PGR (progesterone receptor gene)	Some studies suggest a potential association between this gene and breast cancer [28].
TGF-β (transforming growth factor β)	A cytokine with a definitive role in the development of various cancers, including breast cancer [29, 30].
TNF (tumor necrosis factor)	Although it may exhibit anti-cancer effects, in cancer cells resistant to cell death, TNF promotes angiogenesis, cell migration, and proliferation [31].
CYP19A1	Elevated levels of CYP19A1 mRNA have been detected in women with breast cancer [32].
CLU	The expression of CLU is associated with the development of breast cancer [33].

The expression of genes in various types of breast cancer was analyzed based on the TCGA PanCancer database using RNA sequencing. It was found that most of the studied genes are associated with luminal type A breast cancer. The analysis by Warrier et al. identified numerous genes linked to BPA exposure, providing a foundation for future experimental studies.

PARABENS

Parabens are alkyl esters of p-hydroxybenzoic acid used as antimicrobial preservatives in food, pharmaceuticals, and, as the focus of our work, in cosmetic products [34]. They are used as a preservative, antimicrobial agent, and for extending shelf life. Their advantages include being odorless, biodegradable, stable at various temperatures, under different pH levels, and not affecting the consistency of the product. They are primarily cheap [35]. The most commonly used parabens in the industry are methylparaben (MP), ethylparaben (EP), propylparaben (PP), and butylparaben (BP). Research conducted since 1998 has shown that parabens can act as xenoestrogens, and estrogen plays a crucial role in the development, growth, and progression of breast cancer [8,

36, 37]. In 2004, a study was published describing the presence of parabens in breast tissue in patients with this gland's cancer [8]. The highest concentrations of parabens in the mammary gland were detected in the armpit area, suggesting a connection to the use of cosmetics in this area (deodorants, antiperspirants) [34].

Hager et al. summarized several dozen studies on the relationship between paraben exposure and breast cancer [9]. To determine the correlation between the exposure to the aforementioned compound and the occurrence of breast cancer, the mammary gland tissue had to be examined, and the presence of parabens in this tissue had to be detected. At this point, the authors refer to the above-mentioned study by Barr et al. suggesting that the increased amount of parabens in the outer quadrants of the breast is due to the use of deodorants or antiperspirants in this area. Additionally, it was noted that paraben concentrations are higher primarily in fatty tissue, likely due to the moderate hydrophobicity of these substances. However, the authors do not give a clear answer as to whether parabens are associated with the occurrence of breast cancer [34]. They refer to several studies with varying results: in one study, no association was found between BP or PP levels in serum and breast density [38] (high mammographic breast density is a strong risk factor for breast cancer development) [39], while another study indicates a link between breast cancer occurrence and higher levels of MP, PP, and total parabens in urine with diagnosed cancer [40]. Parabens show estrogenic activity – Wróbel and Gregoraszczuk [41] demonstrated a proliferative effect in MCF-7 breast cancer cells and MCF-10A cells in response to single or repeated exposure to MP, PP, or BP.

Tapia et al. also conducted a study [42] on luminal breast cancer cell lines of West African (HCC1500) and European (MCF-7) origin to better understand the impact of parabens on breast cancer development in Black women. The impact of different doses of MP, PP, and BP on the expression of target genes of the ER was examined. Trefoil factor-1 (TFF1), progesterone receptor (PGR), growth-regulating estrogen receptor binding 1 (GREB1), proto-oncogene MYC (MYC), and cyclin D1 (CCND1) were taken into account. In the HCC1500 cell line, increased expression of TFF1 and PGR was observed. Additionally, it was found that PP and BP could be more estrogenic than MP in luminal breast cancer cells. It was also checked whether these results are specific to cell lines. The results suggest that parabens influence gene regulation in different cell lines – not only HCC1500 and MCF-7 but also BT-474 (European origin) and MDA-MB-175-VII (West African origin). However, the luminal breast cancer cell line of West African origin HCC1500 appears to be more sensitive to parabens than MCF-7. BP also increased cell viability in the HCC1500 line but not in MCF-7. MP and PP did not have such an effect, indicating that BP has a stronger estrogenic effect than these 2 parabens. In summary, the study noted that parabens exhibit similar effects on breast cancer cell lines as estradiol.

However, as a result of an experiment on Sprague-Dawley [43] rats, it was found that exposure to parabens during periods of increased sensitivity to these compounds (perinatal, prepubescent, and puberty periods) causes changes in the histology of the mammary gland (including a decrease in the amount of adipose tissue), which may be associated with the occurrence of breast cancer. Parabens also interact with the human epidermal growth factor receptor 2 (HER2), a receptor involved in intracellular signaling and showing overexpression in a quarter of breast cancer cases. Its ligand is heregulin (HRG). It turns out that together, parabens increase pro-oncogenic c-Myc mRNA expression in BT-474 cells (an ER+/HER2+ breast cancer cell line) [44]. In this regard, HRG acts synergistically with parabens. Despite these study results, the authors conclude that due to the weak affinity of parabens to ERs, their direct link to breast cancer is debatable.

Regarding animal model studies, two more are worth mentioning. The work by Mogus et al. [45] aimed to determine the long-term effects of PP exposure on the mammary gland of pregnant mice. Pregnant BALB/c mice were given PP at doses of 0, 20, 100, or 10,000 μg/kg/24 h during pregnancy. 5 weeks post-involution, mammary glands were collected and examined. In the group of females exposed to 20 PP and 100 PP, a reduced ductal epithelium volume was discovered, indicating that PP reduced the pregnancy effect. The same group also showed an increased number of Ki-67 positive cells, indicative of increased proliferation [46]. This is significant because epithelial stem cell proliferation is a potential factor causing tumor formation in the mammary gland, and a physiological reduction in this proliferation level may be a protective factor against breast cancer. The experiment also involved determining the number of stem cells in the breast post-PP exposure. Several previous studies suggested that parity decreases the number of stem cells in the mammary gland [47, 48], and a reduced number of these cells in the breast post-pregnancy may account for pregnancy's protective effect on breast cancer risk [49]. However, the study results indicate no impact of PP exposure during pregnancy on stem cell colonies. qRT-PCR analysis showed that 20 PP and 10,000 PP affected the nulliparous group. Specifically, TGF-β2 expression increased, and as is known, increased expression of this protein occurs in many cancers, including breast cancer [50]. Thus, it was found that PP reduced the pregnancy effect on the mammary gland, increased stem cell proliferation, and caused minor changes in the expression of ERα receptor-dependent genes.

The study by Tong et al. [51] demonstrated that chronic exposure to parabens, even at low doses (within the "acceptable daily intake for humans" according to the US Food and Drug Administration

[52]), causes an increase in mammary tumor volume and raises the risk of lung metastases from this cancer. The study was conducted on mice given MP and PP from weaning at 28 days postbirth until euthanasia. Paraben doses were chosen to be equivalent to human exposure, i.e., 8.31 mg/kg body weight, which is within the acceptable daily intake. The tumor was then measured 3 times a week from the time it was palpable until it reached a volume of 4 cm^3, at which point the mouse was euthanized. It was found that exposure to MP or PP significantly increased the total tumor volume over time. MP also increased the volume of so-called terminal end buds (TEB), with their physiological regression delayed. This is important because this rapidly proliferating structure is sensitive to carcinogens [53]. Exposure to parabens also increased ER expression in the tumor, promoting the development of luminal breast cancer. Regarding the increased risk of metastasis, parabens, along with the increasing length of the alkyl chain, caused the formation of a functionally altered breast tumor spliceosome. According to some researchers [54], this can lead to a higher risk of breast cancer metastasis. Nevertheless, this study pertains to mice, and its authors express the necessity to confirm such an effect of parabens on malignant breast cancer in humans.

PHTHALATES

Phthalates are esters of phthalic acid considered to be EDCs. Their application depends on the molecular weight of the compound, hence the length of the chain. Long-chain esters, among which DEHP is the most widespread, are plasticizers that impart flexibility to plastic products, including polyvinyl chloride. They are found in food packaging, construction materials, children's toys, and medical products (blood bags, IV drips), as well as in air pollutants, water, and soil [56–59]. Short-chain phthalates are additives in cosmetics and pharmaceuticals [59, 60].

Exposure to these substances results from their widespread use and release from consumer products into the environment. They enter the human body through ingestion, skin contact, and inhalation [59]. Studies on the estrogenic potential of diethyl phthalate (DEP) have shown that despite the lack of direct binding to the ERα receptor, it induces an E2 mimetic effect, as the reactions occurring in the cell are analogous to those triggered by E2 binding to the ERα receptor. In estrogen-dependent ductal breast cancer cells (MCF-7 cell culture), exposure to DEP resulted in the activation of the aforementioned receptor through its phosphorylation at serine 118 (Ser 118). The active receptor integrates nuclear and extranuclear estrogen signals, leading to the activation of cell proliferation pathways, mainly PI3K/AKT, but also ERK/MAPK. Additionally, the expression of cell cycle regulators dependent on the ER mechanism, such as cyclin D1, which influences the G1/S phase transition, was observed [61].

A Danish cohort study investigating the impact of phthalates, including DEP, di(n-butyl) phthalate (DBP), cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), and polyvinyl acetate phthalate (PVAP) contained in pharmaceutical capsules, on breast cancer confirmed a correlation between DBP and breast cancer. DBP accumulated in the body at high concentrations (≥10,000 cumulative mg) is associated with twice the risk of breast cancer, particularly ER-positive cancers, with no link to ER-negative cancers. This observation was stronger in premenopausal women. Lower DBP concentrations and exposure to DEP, CAP, and HPMCP were not associated with breast cancer incidence. The phthalate content in a single capsule shell was estimated to range from 3 µg to 150 mg, depending on the medicinal product [60].

A study by Chen et al. demonstrated that benzyl butyl phthalate (BBP), DBP, and DEHP at doses lower than the acceptable daily intake exhibited proliferative effects through the PI3K/AKT signaling pathway. Synergism between phthalates and E2 was observed, with cells exposed to both showing more pronounced proliferation and ERα expression than when each was administered independently. Additionally, they exhibit anti-apoptotic effects in the presence of E2 by increasing Bcl-2 expression [62]. Studies conducted on the American population indicate a link between DEHP exposure and its metabolites and the occurrence of cancers. It most strongly influenced the development of female and male reproductive system cancers, strongly associated with hormonal action [57].

Phthalate content in the blood serum of healthy women in 2 Mexican cities was examined, revealing higher DEP and lower DBP, DEHP, and BBP concentrations in Mexico City women compared to those in Toluca. In breast cancer patients' blood plasma from Mexico City, contrary to the control group's findings, DBP levels were 25 times higher, while patients in Toluca had higher DEHP and BBP levels. Considering the cancer subtype, DBP and BBP concentrations were higher in HER2+ and TN cancers, not elevated in the ER+ phenotype. Comparing phthalate levels in surviving patients, DEP levels were higher than in the control group, with no significant differences in DEHP levels, and BBP levels were significantly lower. The authors agree that their study results support the hypothesis of a link between phthalates and breast cancer incidence. They also reference preclinical evidence suggesting that breast cancers caused by phthalate exposure occur through ER-dependent and independent signaling. Nonetheless, they emphasize the need to limit phthalate use, thereby reducing environmental contamination with these substances [7].

CONCLUSIONS

Phthalates, parabens, and BPA are widely used chemical compounds that can impact human health, including the development of breast cancer. Phthalates are primarily used as plasticizers in plastic production, parabens are popular preservatives in cosmetics, and BPA is found in many plastic products, such as food containers. Numerous studies indicate that these compounds have endocrine-disrupting properties, meaning they can interfere with the hormonal system.

Research on the impact of these compounds on breast cancer suggests that their long-term exposure may be associated with an increased risk of this cancer. These compounds can mimic the action of estrogens, which play a crucial role in breast cancer development. BPA and phthalates can bind to ERs, potentially leading to uncontrolled breast cell growth. Parabens also exhibit the ability to bind to ERs, which may stimulate cancer development. Moreover, studies have shown that higher concentrations of these compounds in the body may correlate with increased breast tissue density, a risk factor for breast cancer.

In summary, exposure to phthalates, parabens, and BPA may contribute to breast cancer development by disrupting hormonal balance and affecting ERs in breast cells. Although research findings are inconclusive and further analysis is needed, reducing exposure to these compounds, particularly in high-risk individuals, may be a preventive step in reducing breast cancer risk.

ORCID:

Izabela Domańska – https://orcid.org/0009-0003-9348-1287
Aleksandra Sagan – https://orcid.org/0009-0002-6746-4726
Monika Domagała – https://orcid.org/0009-0003-2976-1102
Weronika Duda – https://orcid.org/0009-0002-6242-8785
Emilia Majewska – https://orcid.org/0009-0009-3043-1104
Małgorzata Piśkiewicz – https://orcid.org/0009-0006-0248-1137
Joanna Wiewióra – https://orcid.org/0009-0005-3627-0242

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