



Environmental endocrine disruptors and breast cancer: The role of bisphenols, polychlorinated biphenyls, parabens, and dioxins

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ABSTRACT

Breast cancer is the most common malignancy in women, and environmental factors such as endocrine-disrupting chemicals (EDCs) contribute to its development and progression. This review examines the roles of four major EDCs—bisphenols, polychlorinated biphenyls (PCBs), parabens, and dioxins—integrating mechanistic and epidemiological evidence. A key pathway is the cross-talk between estrogen receptor (ER) and aryl hydrocarbon receptor (AhR), which regulates proliferation, survival, and immune evasion. Bisphenol A (BPA) promotes proliferation, migration, epigenetic reprogramming, and immune escape. PCBs, particularly PCB-153, are linked to metabolic alterations, inflammation, and variable epidemiological associations. Parabens, common in cosmetics, display estrogenic activity and affect oxidative stress, tumor marker expression, and metastasis. Dioxins, especially TCDD, act via AhR to induce inflammation, immunosuppression, and metastasis, with epidemiological links to cancer risk near emission sources. Collectively, these EDCs disrupt hormonal pathways, alter gene expression, and modulate the tumor microenvironment, underscoring the need for further research, regulation, and public health interventions.

1. Introduction

1.1. Breast cancer: an overview

Breast cancer is the most frequently diagnosed cancer in women, with 2,308,897 new cases recorded in 2022, representing 11.6 % of all new cancer cases that year (Bray et al., 2024). It is also the leading cause of cancer-related death in women, accounting for 665,684 deaths and 6.9 % of all cancer-related deaths worldwide in the same year (Arnold et al., 2022). More alarmingly, it is expected that by 2040, there will be 3,000,000 new breast cancer cases annually, representing 40 % of all new cancer cases (Bray et al., 2024). Moreover, breast cancer-related deaths are predicted to account for over 50 % of all cancer-related deaths by 2040, with 1,000,000 deaths annually worldwide (Bray et al., 2024).

Breast cancer is curable in approximately 70–80 % of patients diagnosed at an early, non-metastatic stage of the disease, where the malignancy is confined to the breast or has spread only to auxiliary lymph nodes. However, advanced breast cancer with distant organ metastases remains incurable, with treatment limited to palliative measures to extend survival and alleviate symptoms (Harbeck et al.,

2019).

A wide range of molecular changes can lead to the development of breast cancer, including genetic mutations, gene expression dysregulation and alterations in the tumor microenvironment (Harbeck et al., 2019). While the exact mechanism by which breast cancer initiates remains unknown, extensive research has provided valuable insights regarding the main factors contributing to its development, which results from transforming events in a single cell that are driven by both genetic and epigenetic alterations. Subsequent tumor progression is induced by accumulative additional genetic changes as well as by clonal expansion and selection (Harbeck et al., 2019).

Hormone receptors play a key role in this process, and hormonal imbalances between estrogen and progesterone during each menstrual cycle are believed to enhance cell proliferation and DNA damage. When this repetitive damage is defectively repaired, mutations can render cells pre-malignant, eventually leading to malignancy (Harbeck et al., 2019).

Given the differential expression profiles and other specific characteristics that define breast cancers, numerous classifications have been proposed for the disease. However, the classification most commonly used in clinical practice identifies five surrogate intrinsic subtypes, which are based on the immunohistochemical expression of ER,

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progesterone receptor (PR), and human epidermal growth factor 2 (HER2), as well as on the proliferation marker Ki67 index and tumor histology (Al-Thoubaity, 2020; Yersal and Barutca, 2014). The molecular characteristics and prognosis of these subtypes are described in Table 1.

1.2. Risk factors for breast cancer

Breast cancer is a complex heterogeneous disease that arises from the accumulation and interplay of genetic alterations and environmental factors that alter normal cell function. These risk factors are commonly divided into two groups: non-modifiable and modifiable factors. Non-modifiable factors, which account for 5–10 % of all breast cancer cases, include genetic susceptibility, a family history of breast cancer, other breast diseases, and high breast density (Daly et al., 2021) (Fig. 1). Modifiable risk factors, which account for approximately 90 % of all breast cancer cases (Daly et al., 2021), include obesity, a sedentary lifestyle, reproductive history, hormonal therapies, and environmental exposures such as radiation and xenoestrogens. Among environmental factors, endocrine-disrupting chemicals (EDCs) have emerged as a major concern. EDCs can mimic or antagonize endogenous hormones such as estrogens, while also inducing epigenetic changes, altering immune responses, and reprogramming metabolism—mechanisms that are directly implicated in breast carcinogenesis (Gore et al., 2015). Key challenges in evaluating their role include real-world exposure to complex mixtures (Kortenkamp, 2007), non-monotonic dose–response relationships (Caporale et al., 2022), and heightened vulnerability during critical windows of susceptibility such as puberty, pregnancy, and menopause (Ho et al., 2022).

1.3. The role of estrogens

Estrogens are steroid hormones that play an important role in women's development during different life stages and also contribute to the health of bones, the heart, and the brain in both men and women. They are classified based on their origin, whether they are endogenous (produced by glands or cells of living organisms) or exogenous (derived from synthetic estrogens, foods, or drugs) (Chen et al., 2022). Four types of estrogens have been identified in humans: estrone (E1), 17 β -estradiol (E2), estriol (E3), and estetrol (E4). The general term “estrogen” usually refers to E2 (Fig. 2), as it is the most widely distributed and biologically active estrogen in several tissues and organs. E2 has the highest affinity to ER α , ER β and G protein-coupled ER1 (GPER1, also known as GPR30) and plays an important role in the development of secondary female characteristics, the regulation of the menstrual cycle, and the growth of the endometrial lining from menarche to menopause. In contrast, E1 has a lower affinity to ERs and is the predominant estrogen during menopause. E3 and E4 are mainly present during pregnancy and have lower affinities for ERs compared to E1 and E2 (Chen et al., 2022; Nilsson et al., 2001).

Hormonal exposure is one of the main triggers of sporadic breast cancer. When estrogen binds to the ER, which is located in the nucleus

and encoded by the ER1 (*ESR1*) gene, the ER is activated in a ligand-dependent manner. These hormonal changes occur during mammary gland development in adolescence, at each menstrual cycle, and with pregnancy, leading to hormonal imbalances, particularly between estrogen and progesterone. As a result, during cellular proliferation and repeated occurrence of these hormonal processes, DNA damage can accumulate. Improper DNA repair mechanisms may then result in mutations, ultimately giving rise to precancerous cells (Harbeck et al., 2019).

1.3.1. Canonical ERs

For decades it was believed that only one ER existed. This was later named ER α after a second ER was discovered (ER β) in 1995. Since then, many isoforms of ER β have been identified. The two main ERs, ER α and ER β , are known as canonical receptors and are associated with the effects of estrogen on the cell nucleus. Both ER α and ER β belong to the steroid/thyroid hormone superfamily of nuclear receptors and share a structure composed of three independent but interacting functional domains: NH2-terminal (A/B domain), the DNA-binding domain (C domain), and the ligand-binding domain (D/E/F domain) (Chen et al., 2022; Nilsson et al., 2001) (Fig. 3).

Although the precise mechanism of action of the ERs is not fully defined, it is known that when a ligand binds to the ligand-binding domain either on ER α or ER β , it triggers receptor dimerization, allowing the complex to enter the cell nucleus (Fig. 4). Once in the nucleus, the complex interacts with estrogen response elements (EREs), activator protein-1 (AP-1), and specificity protein-1 (Sp1) on gene promoters, acting as transcription factors that regulate gene expression (Chen et al., 2022; Fuentes and Silveyra, 2019; Nilsson et al., 2001).

The AF-1 ligand-independent activation function is located in the A/B domain, where it participates in the ER protein interaction and target gene expression. This function is highly active in ER α , where it regulates a series of EREs within the promoters of target genes in different cell lines, but it is much less active in ER β . Specifically, ER α facilitates the expression of several potentially oncogenic factors, including V-myc avian myelocytomatosis viral oncogene homolog (MYC), Cyclin D1, forkhead box M1 (FOXM1), growth regulation by estrogen in breast cancer (GREB1), B-cell lymphoma 2 (BCL2), insulin-like growth factor 1 (IGF-1), and C-X-C motif chemokine ligand 12 (CXCL12) (Chen et al., 2022; Fuentes and Silveyra, 2019; Nilsson et al., 2001).

Although ER β is homologous to ER α and interacts with known ER α ligands and transcriptional coregulators, it exhibits different affinities and often leads to distinct functional outcomes. The activity of ER β can vary significantly depending on its isoform, cellular context, and the co-expression of ER α . For instance, in a setting where ER α acts as a proliferative activator, ER β may function as a proliferation inhibitor and apoptosis inducer. Another significant difference between these ERs is where they are primarily expressed. ER α is principally expressed in the uterus, ovaries, bone, white adipose tissue, kidney, liver, and breast. However, ER β is typically found in male reproductive organs, the central nervous system, cardiovascular system, lung, immune system, colon, and kidney (Chen et al., 2022; Fuentes and Silveyra, 2019; Nilsson et al.,

Table 1
Surrogate intrinsic subtypes of breast cancer.

Characteristics	Subtypes				
	Triple- negative	HER2-positive	Luminal B-like HER2-positive	Luminal B-like HER2-negative	Luminal A-like
ER expression	-	-	+	+	++
PR expression	-	-	+	+	++
HER2 expression	-	+	+	-	-
Ki67 index	High	High	High	High	Low
Histology	NST, special type	NST	NST and pleiomorphic	NST, micropapillary and lobular pleiomorphic	NST, tubular cribriform and lobular
Prognosis	Poor	Intermediate	Intermediate	Intermediate	Good

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor 2; NST, no special type.

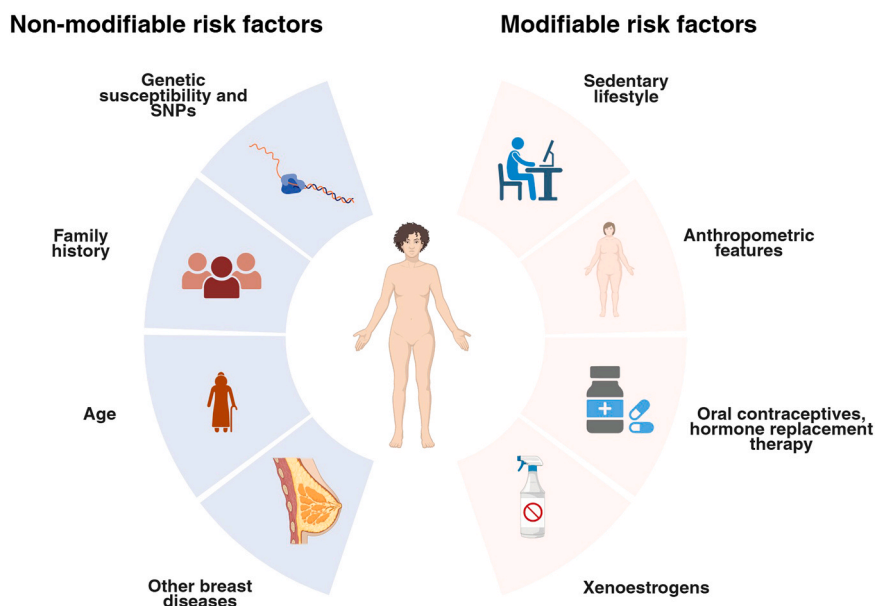


Fig. 1. Summary of risk factors for breast cancer. On the left, most common non-modifiable risk factors. On the right, modifiable risk factors. SNPs: single nucleotide polymorphisms. Created in <https://BioRender.com>.

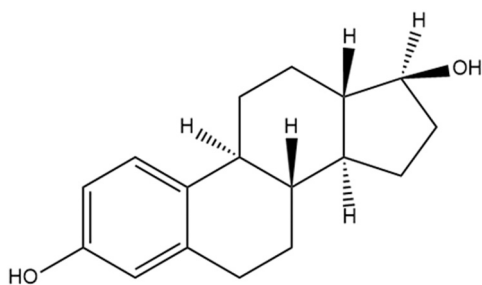


Fig. 2. Chemical structure of 17-β-estradiol. Created with ChemDraw.

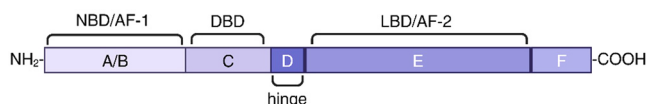


Fig. 3. General structure of estrogen receptors (ERs). AF-1DBD: DNA-binding domain; LBD: ligand-binding domain; NBD: NH₂-terminal domain. Created in <https://BioRender.com>.

2001).

1.3.2. Non-canonical ERs

Non-canonical ERs, such as GPER1, mediate the effects of estrogen through membrane-bound signaling pathways. GPER1 consists of seven transmembrane α -helices, four extracellular segments, and four cytosolic segments. It is primarily found in skeletal muscles, neurons, vascular endothelia, immune cells, and target effector organs. Although active when interacting with estrogens, it has a lower affinity to them than do canonical ERs. The signaling pathway activated by the binding of GPER1 to estrogen causes a non-genomic effect, triggering nuclear transcription factors by changes on ion channel opening or activating enzymes that promote Ca^{2+} mobilization, phosphatidylinositol-3-kinase (PI3K) and mitogen activated protein kinase (Chen et al., 2022; Fuentes and Silveyra, 2019; Nilsson et al., 2001) (Fig. 5).

2. Endocrine disrupting chemicals (EDCs)

EDCs are substances that interfere with the normal functioning of the endocrine system, potentially causing adverse health effects (Colborn et al., 1993). In its 2012 report “State of the Science of Endocrine Disrupting Chemicals”, the World Health Organization (WHO) defines an endocrine disruptor as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations” (<https://www.who.int/publications/i/item/state-of-the-science-of-endocrine-disrupting-chemicals>).

Although there is a wide variety of known EDCs, four types have been extensively studied in relation to breast cancer: bisphenols, polychlorinated biphenyls (PCBs), parabens, and dioxins (Fig. 6). Key findings from *in vitro*, *in vivo*, and epidemiological studies suggest that these compounds influence breast cancer development and progression by disrupting several physiological processes (Koual et al., 2020; Liu et al., 2023; Morgan et al., 2017; Wan et al., 2022). Of note, a growing body of evidence indicates that disruption of ER and aryl hydrocarbon receptor (AhR) signaling constitutes a central mechanism by which EDCs promote breast cancer development (Miret et al., 2023). AhR is a ligand-activated transcription factor that interacts with ER pathways at multiple levels, including direct modulation of ER target genes, competition for co-regulators, and regulation of metabolic and immune-related genes (Puga et al., 2009). Several EDCs exploit this cross-talk to enhance cell proliferation, survival, immune evasion, and epigenetic reprogramming. This ER–AhR signaling interaction has therefore emerged as a unifying framework to understand how diverse chemical exposures converge to influence breast cancer initiation and progression (Miret et al., 2023; Safe et al., 2013).

In this review, we focus on four major EDC classes—bisphenols, PCBs, parabens, and dioxins—because they represent compounds with widespread human exposure, substantial epidemiological and experimental evidence linking them to breast cancer, and well-characterized activity as ER and/or AhR ligands. While other EDCs such as per- and poly-fluoroalkyl substances (PFAS), organophosphate flame retardants (OPFRs), and organochlorine pesticides are also of significant concern, these four groups were selected as representative paradigms to illustrate both shared and distinct mechanisms of breast cancer development and progression. By offering a comparative analysis of these high-exposure

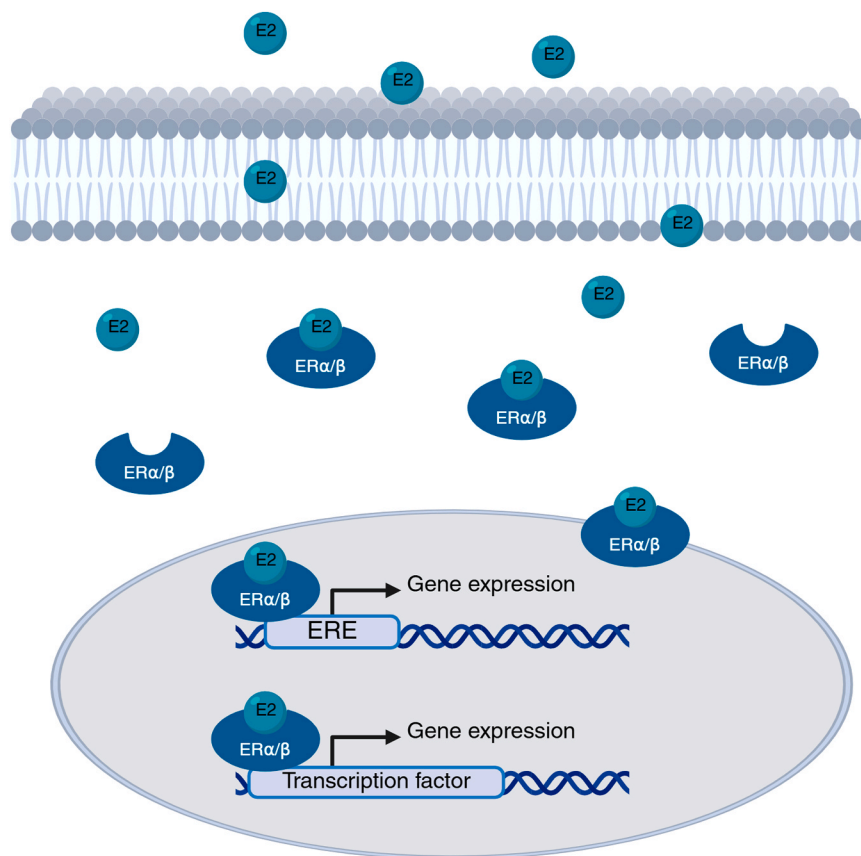


Fig. 4. Genomic effects of oestrogen binding to estrogen receptor (ER) α or ER β . Upon binding to 17 β -estradiol (E2), ER α and ER β interact with estrogen response elements (EREs) to regulate gene transcription. Created in <https://BioRender.com>.

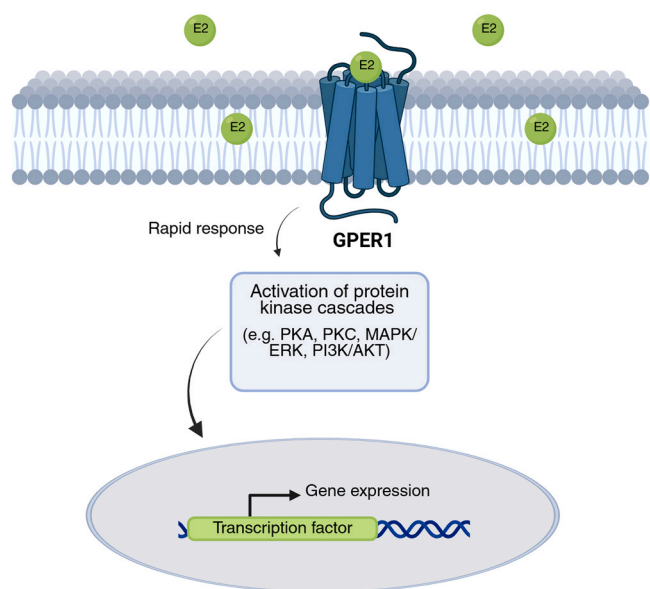


Fig. 5. Non-genomic effects of oestrogen mediated by membrane-associated estrogen receptors (ERs), such as GPER1. Binding to 17 β -estradiol (E2) activates various intracellular signalling pathways, including PKA (protein kinase A), PKC (protein kinase C), MAPK/ERK (mitogen-activated protein kinase/extracellular signal-regulated kinase), and PI3K/AKT (phosphatidylinositol 3-kinase/Akt). Created in <https://BioRender.com>.

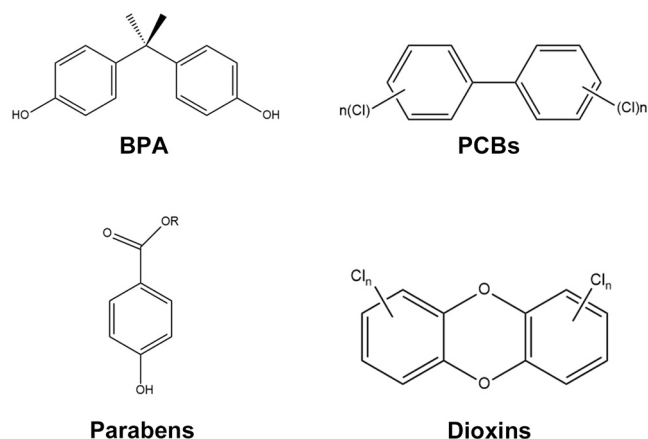


Fig. 6. Chemical structures of bisphenol A (BPA), polychlorinated biphenyls (PCB), parabens and dioxins. Created with ChemDraw.

EDC classes, our review provides added value over previous summaries by integrating emerging evidence on ER/AhR cross-talk as a central unifying pathway, and by highlighting recent advances in epigenetic regulation, metabolic reprogramming, and tumor microenvironment modulation.

2.1. Bisphenols and breast cancer

Bisphenols, particularly bisphenol-A (BPA), have been at the forefront of EDC research due to their widespread use and potential implications for human health. BPA is a synthetic organic compound of the

phenol family, characterized by hydroxyl groups directly attached to aromatic rings (Fig. 6). It is extensively used in the production of polycarbonates and epoxy resins, which are key components in thermal paper, food and beverage containers, medical equipment, and electronics. Human exposure occurs primarily through ingestion, as BPA can leach into food and beverages when containers are exposed to high temperatures or extreme pH. Additional routes of exposure include dermal absorption and inhalation (Keshavarz-Maleki et al., 2021). Once internalized, BPA accumulates in adipose tissue—particularly breast adipose tissue—due to its lipophilic nature. Though urinary BPA levels reflect recent exposure, its concentration in adipose tissue may serve as a biomarker for chronic exposure (Keshavarz-Maleki et al., 2021; Reeves

et al., 2018).

Fig. 7 and Table 2 summarize the sources and effects of BPA exposure in breast cancer development and progression as determined through *in vitro*, *in vivo*, and patient studies. BPA binds to both canonical and non-canonical ERs and has thus been extensively studied in the context of breast cancer. Numerous preclinical studies have shown that BPA promotes tumor proliferation and migration and genomic instability (Stillwater et al., 2020). Awada et al. (2019) observed that BPA exposure increased metabolic activity and cell cycle progression in MCF-7 breast cancer cells in a time- and dose-dependent manner mediated by ERs. Additionally, BPA enhanced cell migration and upregulated DNA methyltransferase 1 (DNMT1), suggesting a role in epigenetic

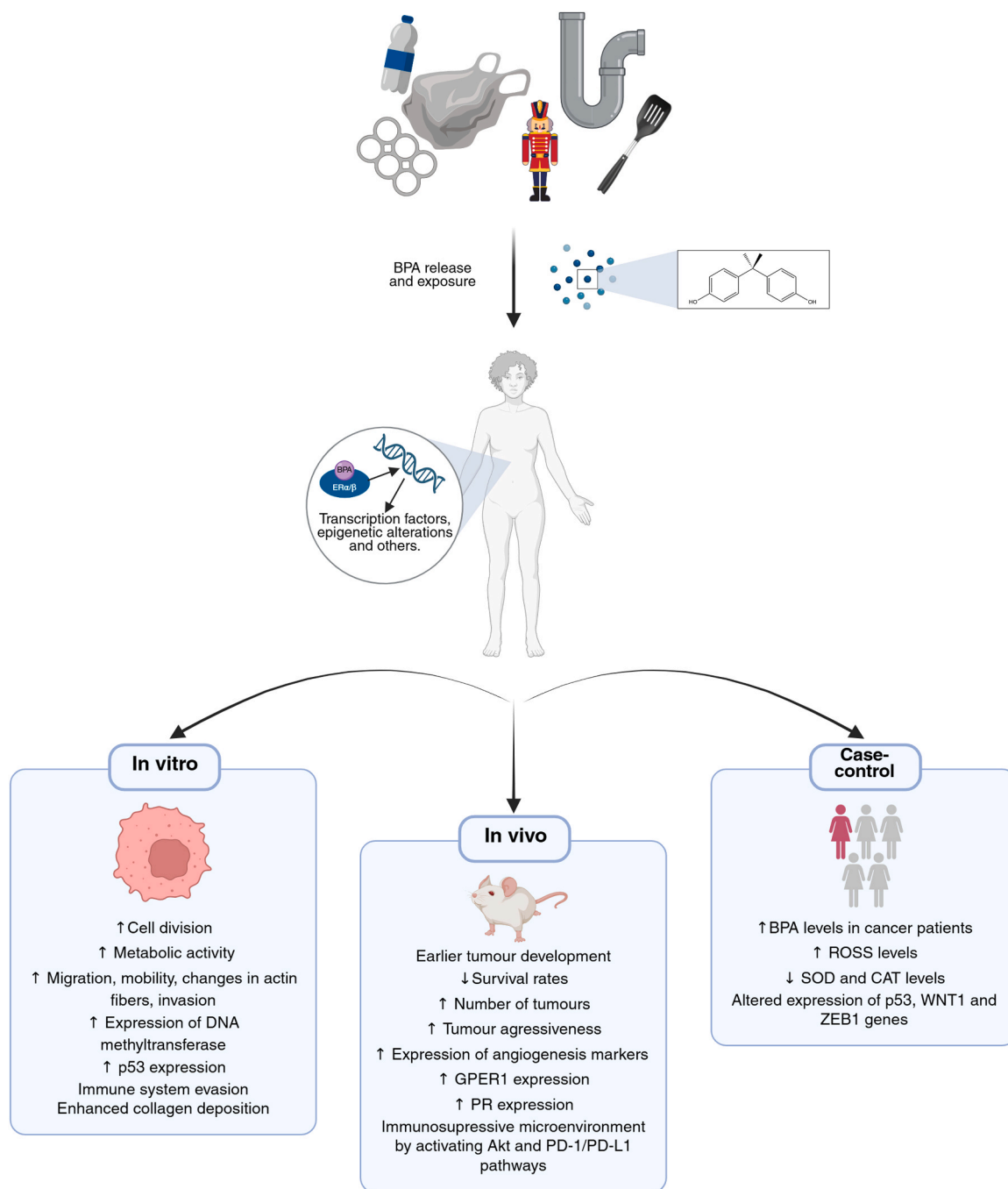


Fig. 7. BPA and breast cancer. BPA exposure has demonstrated diverse effects in *in vitro*, *in vivo*, and case-control studies. BPA: bisphenol A; CAT: catalase; GPER1: G-protein coupled estrogen receptor (also known as GPR30); PD-1: Programmed death 1; PD-L1: Programmed ligand receptor 1; PR: Progesterone receptor; ROS: Reactive oxygen species; SOD: Superoxide dismutase. Created in <https://BioRender.com>.

Table 2
Mechanistic overview of bisphenols, PCBs, parabens, and dioxins in breast cancer development and progression.

EDC class	Primary receptors	Key pathways	reast cancer-related effects	In vitro	In vivo	In humans	References
Bisphenols (BPA, BPS, BPF)	ERα/ERβ GPER1	PI3K/PTEN/AKT c-MYC	Proliferation Migration and invasion	✓	✓	Δ	(Awada et al., 2019; Bhan et al., 2014; Boszkiewicz et al., 2020; Del Favero et al., 2024; Doherty et al., 2010; Dong et al., 2025; Donini et al., 2020; Focaccetti et al., 2024; Ishtiaq et al., 2023; Kim et al., 2017; Kwon, 2022; Lloyd et al., 2019)
	AhR cross-talk	Oxidative stress Epigenetic alterations (EZH2/H3K27me3, HOTAIR) NF-κB Upregulation of invasion-related genes	EMT Inflammation Immune evasion Therapy resistance; Metabolic alterations				
PCBs (DL, NDL)	AhR (DL) ER (NDL)	CYP1A1/1B1 ILA/ILB/NF-κB	Proliferation Migration and invasion	✓	Δ	Δ	(Amadou et al., 2021; Curtis et al., 2019; Desnavailles et al., 2024; Deygas et al., 2021; Fiolet et al., 2022; Goodman et al., 2022; Leng et al., 2016; Morin et al., 2022; Parada et al., 2020; Qin et al., 2022)
		Oxidative stress GLUT1 upregulation Epigenetic alterations (DNA methylation)	Inflammation Immune modulation Metabolic alterations				
Parabens (MP, EP, PP, BP)	ERα/Erβ AhR (chlorinated parabens)	ER target reprogramming	Proliferation Migration and invasion	✓	Δ	Δ	(Boberg et al., 2010; Dairkee et al., 2023; Elsehly et al., 2022; Guzel Bayulken and Ayaz Tuyulu, 2019; Nowak et al., 2019, 2018)
		Oxidative stress Genotoxicity and cytotoxicity Epigenetic alterations (DNA methylation)	EMT Immune modulation Inflammation				
Dioxins (TCDD)	AhR	CYP1A1/1B1 and ALDH1A3 overexpression	Immunosuppression	✓	✓	Δ	(Degner et al., 2009; Koual et al., 2020; Papoutsis et al., 2012, 2010; Patrizi and Siciliani de Cumis, 2018; Rhee et al., 2023; Shan et al., 2020; Sweeney et al., 2022; Tomblin et al., 2016; VoPham et al., 2020)
	EGFR inhibition	Pro-inflammatory chemokines/ NF-κB	Migration and invasion Metastasis/EMT				
		Epigenetic alterations (BRCA1 methylation, histone marks) LAT1 overexpression	Inflammation Therapy resistance Metabolic reprogramming				

AhR, aryl hydrocarbon receptor; BP, butylparaben; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; DL, dioxin-like; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; EP, ethylparaben; ER, estrogen receptor; GPER, G protein-coupled ER1; MP, methylparaben; NDL, non-dioxin-like; PP, propylparaben; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin. ✓: evidence available; Δ: limited or inconsistent evidence

alterations that affect cancer-related pathways, such as focal adhesion and the cGMP–PKG signaling pathway (Awada et al., 2019). In line with these findings, BPA engaged epigenetic mechanisms in mammary tissue and breast cancer models. Developmental exposure increased EZH2 and the repressive histone mark H3K27me3 in mouse mammary gland, producing long-lasting epigenomic reprogramming (Doherty et al., 2010), while in ER-positive breast cancer cells BPA induced the oncogenic long non-coding RNA HOTAIR — a key player in gene silencing and breast cancer — via ER-coregulator recruitment and promoter chromatin remodeling (Bhan et al., 2014). These changes aligned with increased mammary tumor susceptibility after perinatal BPA exposure. Lloyd et al. (2019) reported that BPA increased p53 expression and cell proliferation while downregulating ERα, indicating that BPA may also exert effects via the c-Myc oncogene, a key regulator of cellular growth and metabolism (Lloyd et al., 2019). Del Favero et al. (2024) further demonstrated that BPA increased cell mobility in both MCF-7 and MDA-MB-231 cells, accompanied by cytoskeletal reorganization and upregulation of the invasion-related genes integrin β1 and cathepsin D (Del Favero et al., 2024). The effects of BPA are not limited to ERα; it also modulates the activity of ERβ, which may act as either a tumor suppressor or promoter depending on isoform expression and context. BPA disrupted ERβ’s protective function by altering gene expression patterns and shifting the ERα/ERβ balance (Hirao-Suzuki, 2021). Interestingly, preclinical evidence has further elucidated the role of BPA in breast carcinogenesis through AhR-dependent pathways. Donini et al. (2020) demonstrated that chronic low-dose BPA exposure in mammary epithelial cells promotes a more aggressive phenotype via functional

cross-talk between AhR and the G protein–coupled receptor GPR30. Notably, an AhR/GPR30 gene expression signature was also associated with poor prognosis in ER-negative and triple-negative breast cancers (Donini et al., 2020).

In vivo studies using BALB-neuT mice—a transgenic model predisposed to mammary carcinomas—revealed that BPA exposure through drinking water accelerated tumor onset (week 12 vs. week 16), increased tumor burden, and shortened survival. Although ERα expression was low in the tumors, GPER1 was highly expressed during both pre-invasive and invasive stages, suggesting that it may mediate BPA’s effects in ER-negative breast cancers. BPA-treated mice also exhibited higher levels of PR, Ki67, and CD31, along with activation of the Akt pathway and increased PD-1/PD-L1 expression. These findings indicate an immunosuppressive microenvironment, with elevated regulatory T cells and exhausted T lymphocytes (Focaccetti et al., 2024). Kwon et al. expanded on these findings by showing that BPA not only promotes proliferation via ERs but also disrupts immune cell function and increases collagen deposition, leading to mammary gland stiffness and further activation of the Akt pathway. Moreover, BPA also induced epigenetic modifications favoring adipocyte differentiation and chronic inflammation, both of which contribute to a pro-tumorigenic microenvironment (Kwon, 2022).

The influence of BPA on the tumor microenvironment has also been studied in relation to adipocytes. A cross-sectional study reported a higher incidence of hormone-related cancers in individuals with a body mass index (BMI) ≥ 30 who had detectable BPA exposure (Dong et al., 2025). Experimental data showed that BPA-exposed 3T3-L1

pre-adipocytes differentiated into cancer-associated adipocytes (CAAs), evidenced by increased lipid accumulation, elevated leptin and adiponectin expression, and decreased levels of the tumor suppressor PTEN. This resulted in activation of the PI3K/Akt pathway, promoting breast cancer cell migration and invasion. *In vivo* xenograft models in BALB/c mice confirmed these findings, as BPA-induced CAAs enhanced tumor growth (Dong et al., 2025).

Moreover, BPA can interfere with breast cancer treatment. *In vitro* studies found that BPA can reduce the efficacy of tamoxifen and other cytostatic therapies (Boszkiewicz et al., 2020). Finally, in a recent epidemiological study, Ishtiaq et al. (2023) compared BPA serum levels in breast cancer patients and healthy controls. Levels were significantly higher in patients, who also exhibited increased oxidative stress markers,

including elevated ROS, and decreased antioxidant enzymes like SOD and CAT. They further reported altered expression of cancer-related genes, including WNT1, and ZEB1, as well as increased p53 expression at both mRNA and protein levels, suggesting that BPA could induce DNA damage via oxidative stress. Lifestyle factors, such as frequent consumption of canned foods and use of plastic containers, were associated with higher BPA levels, highlighting the importance of behavior and environmental factors in breast cancer risk (Ishtiaq et al., 2023) (Fig. 7 and Table 2).

Although BPA has been the most extensively studied bisphenol, increasing attention has recently turned to its structural analogues, bisphenol S (BPS) and bisphenol F (BPF), which are widely used as BPA substitutes. Accumulating evidence implicates BPS and BPF in mechanisms relevant to breast cancer. In ER-positive MCF-7 models, both BPS and BPF were found to stimulate proliferation, migration, and epithelial-mesenchymal transition (EMT), mirroring BPA's effects (Kim et al., 2017). At the tissue level, exposure of human mammary organoids to low-nanomolar BPS/BPF disrupted organoid architecture, increased supernumerary branching, and shifted the proteome toward pro-tumorigenic signatures (Winkler et al., 2022). Mechanistically, BPS and BPF bind ERs and exhibit estrogenic activity that is not only comparable but, in some studies, even greater than BPA, while transcriptome profiling in ER-positive cells showed that BPA alternatives re-engaged estrogen-responsive gene programs (Rochester and Bolden, 2015). Moreover, in a study of a zebrafish model, bisphenol AF (BPAF) showed higher toxicity and estrogenic activity than BPA, which had been expected to be more harmful (Moreman et al., 2017).

2.2. PCBs and breast cancer

PCBs are organochlorinated compounds composed of two benzenic rings with one to ten chlorine atoms, resulting in 209 distinct congeners (Fig. 6). Their exceptional thermal stability and resistance to combustion led to widespread use throughout the 20th century in various industrial and commercial applications. However, once their toxic and carcinogenic activity became evident, increasing concerns prompted their prohibition in 1986 (Zani et al., 2013). Nonetheless, PCBs are still present in the environment and in older equipment and materials produced before the ban was implemented. As persistent organic pollutants, PCBs remain stable for decades in environmental matrices such as air, water, soil, and biota, contributing to continued human exposure through multiple routes, including ingestion of contaminated fatty foods, inhalation, dermal contact, and transmission from mother to child via placenta or breastfeeding. Moreover, like BPA, PCBs accumulate in adipose tissue (Carpenter, 2006).

PCBs are commonly classified into three groups based on structure and mechanism of action, and also into dioxin-like and non-dioxin-like congeners (Safe, 1994). Dioxin-like PCBs act as AhR agonists, and AhR activation directly cross-talks with ER signaling, thereby influencing gene transcription programs that regulate cell proliferation, apoptosis, and immune responses. Epidemiological evidence indicates that dioxin-like congeners, through AhR activation and ER cross-talk, may be

more strongly associated with breast cancer risk and poorer prognosis compared with non-dioxin-like congeners, although epidemiological findings remain heterogeneous (Parada et al., 2020; Zhang et al., 2015).

Fig. 8 and Table 2 summarize the sources and effects of PCB exposure in breast cancer development and progression. Since the prohibition of PCB production, many governments have set themselves the objective of eliminating PCBs from existing contaminated machinery. However, exposure to these compounds persists and can lead to the development of breast cancer. PCB-153 is the most commonly detected congener in environmental samples and a major contributor to human PCB body burden estimates (Fernandez et al., 2008). A recent analysis of data from the XENAIR case-control study, which is part of the French E3N prospective cohort study (Amadou et al., 2021; Deygas et al., 2021), revealed that the group with the highest PCB-153 concentrations had a 69 % greater likelihood of developing breast cancer than the group with the lowest concentrations (Desnavailles et al., 2024). In contrast, a follow-up cohort study of Japanese patients involved in the 1968 Yusho incident, who were accidentally exposed to high levels of PCBs and dioxins through ingestion of contaminated rice oil, showed no significant positive association between exposure to these contaminants and increased breast cancer-related death (Onozuka et al., 2020). In line with these findings, a cohort study in nine European countries found no significant association between reported dietary exposure to PCBs and dioxins and breast cancer incidence (Fiolet et al., 2022).

In addition, PCB29-pQ, a PCB quinone-type metabolite, was discovered to have the ability to promote aerobic glycolysis, an important marker of metabolic reprogramming in cancer progression. Qin et al. (2022) reported that PCB29-pQ exposure in breast cancer MDA-MB-231 cells was associated with upregulation of the glucose transporter (GLUT1) and other key enzymes involved in aerobic glycolysis. Moreover, PCB29-pQ increased cell migration and invasion *in vitro* and in female BALB/c mouse models (Qin et al., 2022).

The influence of PCBs on gene expression was also studied by Morin et al. (2022), who explored the effect of PCB126 on gene expression in primary benign breast epithelial cells (HBECs) and patient-derived explants. They found that PCB126 significantly modified the expression of 144 genes. CYP1A1, CYP1B1, interleukin 1 alpha (IL1A), interleukin 1 beta (IL1B), and amphiregulin (AREG) were among the upregulated genes. CYP1A1 and CYP1B1 are regulated by the AhR and play a key role in the detoxification and metabolism of xenobiotics. IL1A and IL1B encode pro-inflammatory cytokines involved in immune signaling. AREG is a growth factor associated with cell proliferation and epithelial signaling. Downregulated genes included matrix metalloproteinase 7 (MMP7) and C-C motif chemokine ligand 28 (CCL28). MMP7 is linked to epithelial homeostasis and tissue remodeling, while CCL28 is related to immune regulation and lymphocyte chemotaxis (Morin et al., 2022).

Beyond their role as endocrine disruptors, PCBs have also been shown to induce epigenetic alterations, including DNA methylation, histone modifications, and changes in noncoding RNA expression, potentially promoting carcinogenic processes (Goodman et al., 2022). Studies indicate that the epigenetic effects of PCBs depend on their congener type, with non-dioxin-like PCBs generally promoting hypermethylation, whereas dioxin-like congeners tend to induce hypomethylation (Singh, 2024). Consistently, an epigenome-wide association study in a US population reported that PCB exposure was correlated with differential DNA methylation at over 1300 CpG sites, particularly in promoter regions linked to xenobiotic metabolism and immune function (Curtis et al., 2019). Furthermore, congener-specific epidemiological analyses highlight that elevated levels of non-dioxin-like congeners such as PCB-99, PCB-183, and PCB-187 are associated with increased breast cancer risk, suggesting that epigenetic modulation may underlie these associations (Leng et al., 2016).

2.3. Parabens and breast cancer

Parabens are esters of P-hydroxybenzoic acid with various alkyl

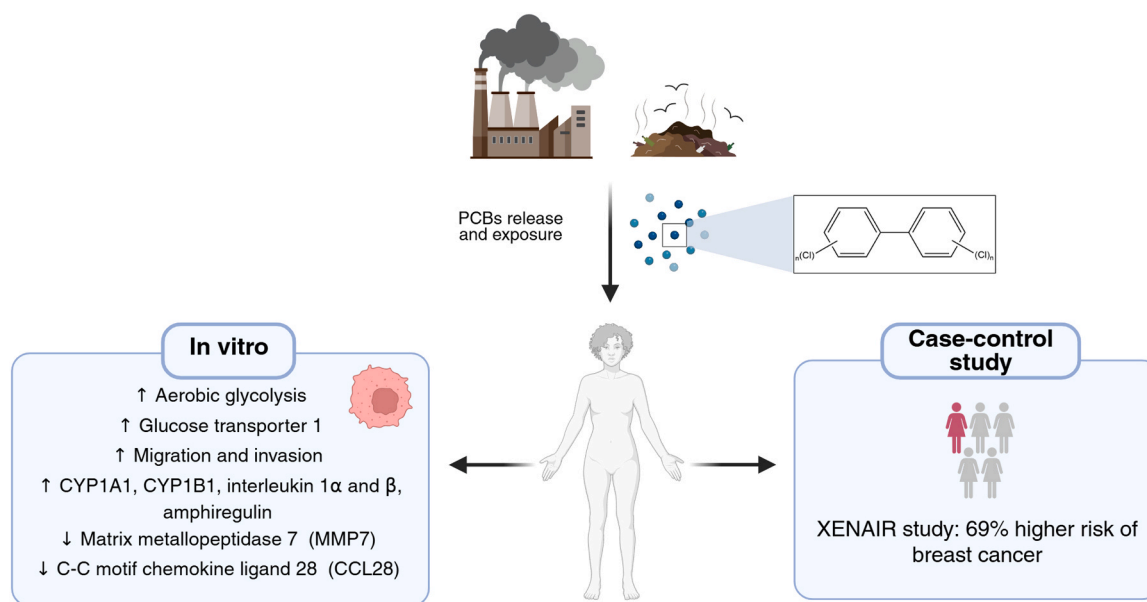


Fig. 8. PCB and breast cancer. PCB exposure has shown multiple effects *in vitro* that are associated with the promotion and progression of breast cancer. Created in <https://BioRender.com>.

chain lengths (Chatterjee et al., 2024; Nowak et al., 2018) (Fig. 6). They are widely used in personal care products, such as lotions and deodorants, as well as in pharmaceutical products, clothes, and food, to prevent the growth of unwanted microorganisms (Li et al., 2023). This extensive use of parabens makes exposure through dermal absorption or gastrointestinal uptake very likely. Parabens can then be distributed systemically throughout the body and have been detected in human tissues, blood, breast milk, placenta, and urine (Hager et al., 2022; Park et al., 2019). Those most frequently detected in biological fluids are methylparaben (MP), ethylparaben (EP), propylparaben (PP), and butylparaben (BP) (Hager et al., 2022; Nowak et al., 2018).

Their widespread and nearly unavoidable presence in daily life has made parabens a particular focus of research. In human skin, small intestine, and liver, parabens undergo hydrolysis by esterases, which converts them into p-hydroxybenzoic acid. The rate of this reaction increases in proportion to the length of the paraben side chain. Consequently, MP, which has the shortest side chain, is the most abundant in biological fluids, where it remains largely intact (Ye et al., 2006). Intact parabens that evade first-pass metabolism by esterases can bind to serum albumin, which protects them from further metabolism and facilitates their distribution and bioaccumulation (Obringer et al., 2021).

Fig. 9 and Table 2 summarize the sources and effects of paraben exposure in breast cancer development and progression. Parabens regulate ER-mediated gene expression *in vitro*, and *in silico* simulations have shown that MP and EP interact in what seems to be a spontaneous manner with two key amino acids in the ligand-binding pocket of ERs (Nowak et al., 2018). Additionally, all types of parabens exhibit similar affinities for ERs when administered at certain doses, and when different parabens are administered at the same dose, those with a longer alkyl chain induce the highest estrogenic activity (Tong et al., 2023). In line with these receptor-mediated actions, parabens also influence epigenetic regulation in breast cancer by modulating risk in a DNA methylation-dependent manner and reprogramming ER-regulated transcription. In a population-based study, higher urinary paraben levels were associated with increased breast cancer risk specifically among women with reduced global DNA methylation and with tumors showing gene-specific promoter hypomethylation, indicating that DNA methylation status modulates the relationship between paraben exposure and breast cancer risk (Parada et al., 2022). The estrogenic and anti-spermatogenic activity of parabens was observed in a study of adult

zebrafish. After MP and PP were administered to the zebrafish, they developed testicular malformations and alterations, including impaired germ cell development and multinucleated monocytes, suggesting that parabens may play a significant role in upregulating ERs and down-regulating the androgen receptor (AR) (Bereketoglu and Pradhan, 2019). Notably, some parabens may also act through AhR-related pathways. In aquatic toxicology studies, several chlorinated parabens structurally similar to hydroxylated PCBs were shown to activate AhR in yeast reporter systems and human HepG2 cells, inducing CYP1A1 activity (Terasaki et al., 2015). These findings suggest that certain paraben derivatives could contribute to breast carcinogenesis not only via ER signaling but also through AhR-mediated mechanisms.

On the other hand, parabens have also been shown to modulate inflammatory and immune pathways relevant to breast cancer. *In vitro* and *in vivo* studies have reported that some parabens can modulate cytokine expression and immune-related gene networks, contributing to a pro-inflammatory microenvironment and to immune dysregulation with impaired tumor surveillance (Boberg et al., 2010; Nowak et al., 2019). In this context, Bayülken & Tüylü (2019) demonstrated that several paraben esters (butyl-, propyl-, isobutyl-, and isopropylparaben) exert genotoxic and cytotoxic effects on human peripheral lymphocytes, as evidenced by increased sister chromatid exchanges, chromosomal aberrations, and micronucleus formation (Guzel Bayulken and Ayaz Tuylu, 2019). Since lymphocytes play a critical role in recognizing and eliminating transformed cells, their impairment by parabens could facilitate tumor immune evasion, thereby contributing to breast carcinogenesis. Consistently, epidemiological data suggest associations between paraben exposure, oxidative stress, and immune suppression in breast cancer (Wan et al., 2022).

Based on the proven affinity of parabens to ERs, Elsehly et al. (2022) further investigated the role of MP role in promoting tumorigenic behavior in MCF-7 breast cancer cells. In MCF-7 cells exposed to MP, they observed several changes: increased viability in a concentration- and time-dependent manner; a dose-dependent increase in Ki-67 expression; a remarkable increase in E2 secretion, particularly at high doses; a significant increase in early apoptosis at various concentrations; reduced lipid peroxidation (based on malondialdehyde levels); an increased total antioxidant capacity; and a significantly decreased oxidative stress index with a strong negative correlation with cell viability (Elsehly et al., 2022). A recent study in zebrafish showed that

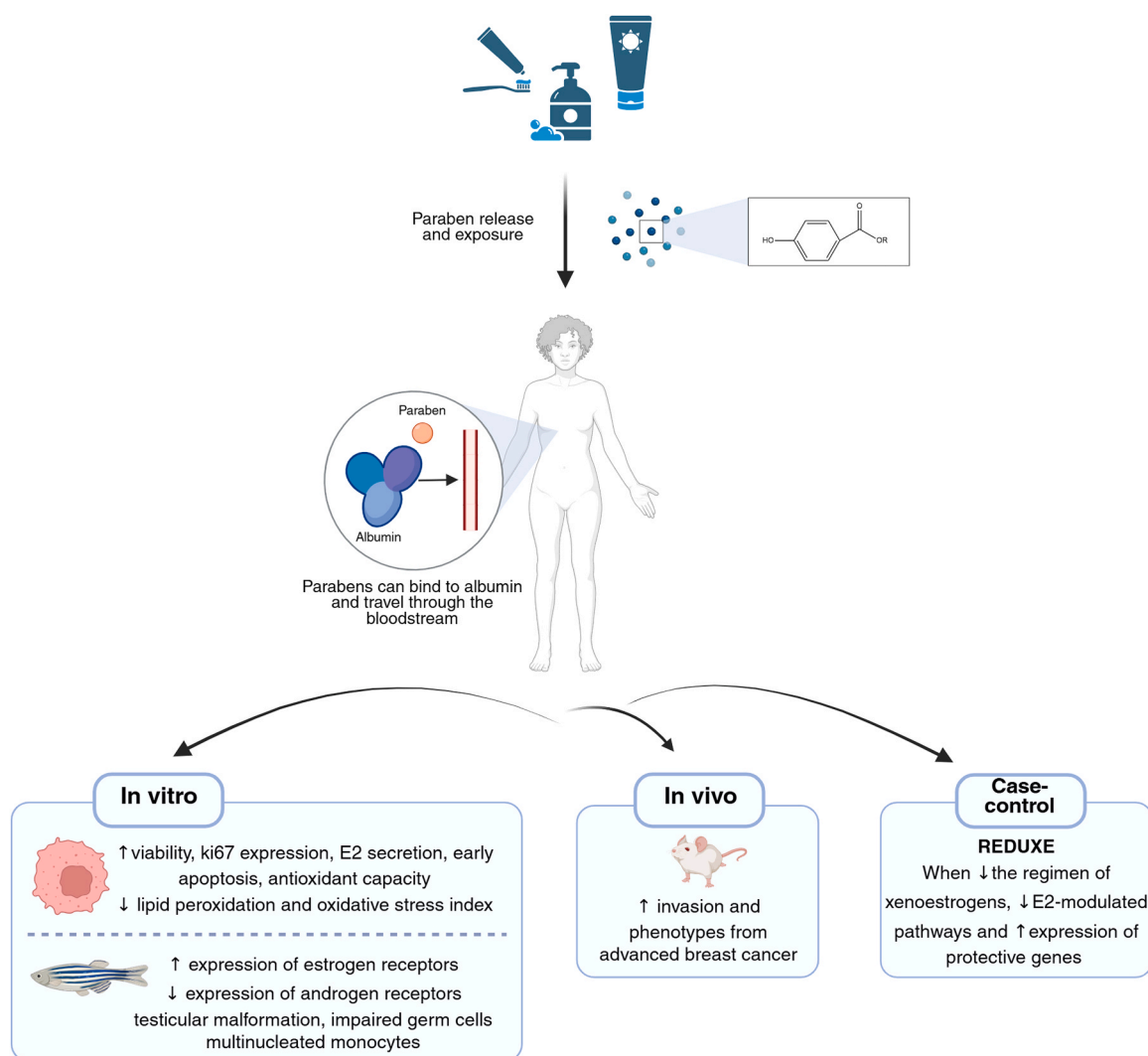


Fig. 9. Parabens and breast cancer. Parabens can modulate several molecular pathways involved in breast cancer development and progression. E2: 17 β -estradiol. Created in <https://BioRender.com>.

exposure to PP and MP decreased the expression of several genes related to oxidative stress (Bereketoglu and Pradhan, 2019). A similar study analyzing the effects of MP and PP in mice found that although the number of new tumors in MP/PP-treated mice did not reach statistically significant levels compared to the control group, there was a qualitative – though not significant – increase in tissue invasion. Moreover, the paraben-exposed mice developed cancer phenotypes associated with advanced pathological stages in human breast cancer, including a significant increase in total mammary tumor volume over time and an increased number of pulmonary metastases per week (Tong et al., 2023).

A different approach was taken by Dairkee et al. (2023) to explore the role of EDCs in the development of breast cancer. In their REDUXE study, volunteers followed a regimen of reduced exposure to parabens and other xenoestrogens, and the differences in breast tissue characteristics before and after the REDUXE regimen were analyzed (Dairkee et al., 2023). Interestingly, after the REDUXE regimen, the expression levels of genes typically associated with cancer were found to have decreased and returned to levels associated with normal tissue. Specifically, levels of toll-like receptor 4 (TLR4), myeloid differentiation primary response 88 (MYD88), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) showed greatly reduced expression levels. In addition, expression levels increased in minichromosome maintenance complex component 7 (MCM7) and in the tumor suppressor mothers against decapentaplegic homolog 4 (SMAD4).

Additionally, 17 genes associated with the E2-modulated pathway were differentially expressed between the volunteers following the REDUXE regimen and controls; six were downregulated and 11 upregulated (Dairkee et al., 2023).

2.4. Dioxins and breast cancer

Dioxins are persistent organic pollutants that are generated during industrial processes like waste incineration, chemical manufacturing, and herbicide production. Dioxins are characterized by the presence of two benzene rings connected by a pair of oxygen atoms. Additionally, chlorine atoms can be paired with carbon atoms that are not bonded to oxygen, which increases toxicity (Mandal, 2005) (Fig. 6). Like other EDCs, dioxins are highly lipophilic, which allows them to accumulate in adipose tissue, and are also extremely environmentally persistent. Dioxins accumulate in the food chain, primarily in animal adipose tissue, and require the activation of the xenobiotic receptor AhR and cytochrome P450 enzymes to exert their toxic effects (Denison and Nagy, 2003; Mandal, 2005).

Fig. 10 and Table 2 summarize the sources and effects of dioxin exposure in breast cancer development and progression. Individuals can be exposed to dioxins by ingesting contaminated food, breathing polluted air, or touching contaminated surfaces. Exposure to especially high doses of dioxins is likely if an individual works in an environment

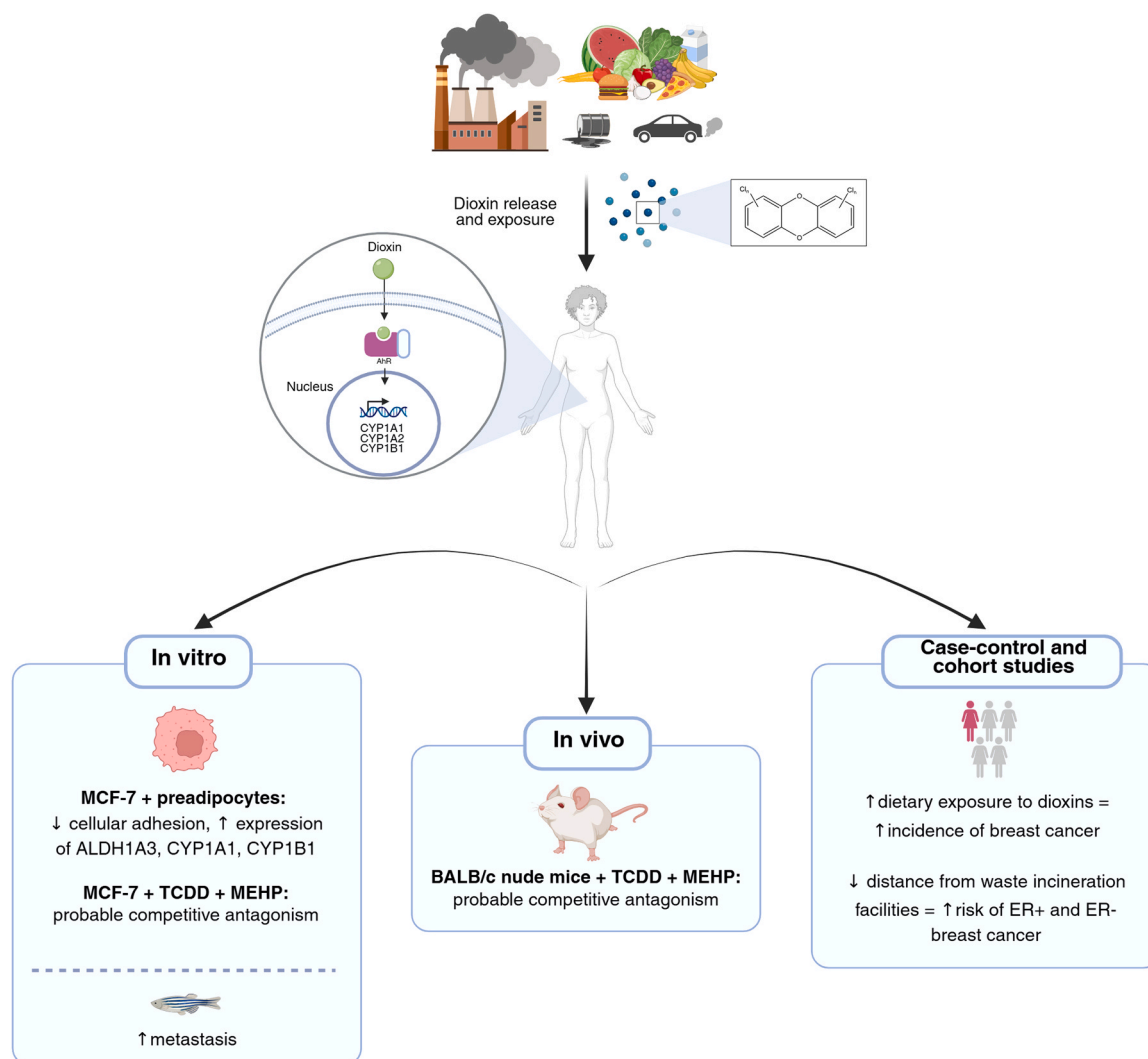


Fig. 10. Dioxins and breast cancer. Once inside the body, dioxins bind to the AhR in the cytoplasm, forming a ligand-receptor complex. This complex translocates to the nucleus, where AhR functions as a transcription factor, inducing the expression of the CYP450 gene. AhR: Aryl hydrocarbon receptor; ALDH1A3: Aldehyde dehydrogenase 1 family member A3; CYP1A1: Cytochrome P450 family 1 subfamily A member 1; CYP1A2: Cytochrome P450 family 1 subfamily A member 2; CYP1B1: Cytochrome P450 family 1 subfamily B member 1; ER+ : Estrogen receptor-positive; ER-: Estrogen receptor-negative; MCF-7: Michigan Cancer foundation-7 breast cancer cell line; MEHP: Mono(2-ethylhexyl) phthalate; TCDD: 2,3,7,8-Tetrachlorodibenzo-p-dioxin. Created in <https://BioRender.com>.

where high concentrations are produced, is affected by the accidental release of dioxins, or lives near municipal waste incinerators (Fiedler, 1996; Mandal, 2005). Due to their persistence and bioaccumulation, dioxins pose serious health risks and have been classified as group I carcinogens by the WHO International Agency for Research on Cancer (IARC) (<https://monographs.iarc.who.int/agents-classified-by-the-iarc>). In 2005, the WHO introduced the term “toxic equivalency factor” (TEF) to categorize the relative toxicity of dioxins, dibenzofurans and dioxin-like PCBs in comparison with the most biologically active toxic form of dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). The TEF values were reevaluated in 2022 (<https://www.who.int/news/item/15-03-2024-who-expert-consultation-on-updating-the-2005-toxic-equivalency-factors-for-dioxin-like-compounds-including-some-polychlorinated-biphenyls>). However, some classifications, especially for certain PCBs, remain unreliable due to lack of data. Nevertheless, it is estimated that by applying the newly proposed TEF criteria, the toxic equivalence in several food products would decrease by approximately 50 % (DeVito et al., 2024).

Since human exposure to dioxins is primarily through the ingestion of food, Shi et al. (2024) assessed dietary dioxin exposure and its association with cancer risk and disease burden in China. Although they

found that dioxin levels in food decreased between 2000 and 2020, in specific regions, dioxins remained at high concentrations. The group with the highest exposure was children aged 0–14 years, who also had the highest associated cancer risk. Interestingly, the cancer burden attributable to dietary dioxins was higher in males than in females, with prostate cancer being the most frequent type in men and breast cancer in women (Shi et al., 2024). In another study exploring the effects of dioxins in the air, a prospective cohort study in non-occupationally exposed U.S. women revealed that dioxin emissions from municipal solid waste incinerators located 3–10 kms from their residences were significantly associated with an increased risk of invasive breast cancer, including both ER-positive and ER-negative subtypes (VoPham et al., 2020). In the same line, another prospective cohort study examined the association between living near dioxin-producing industrial facilities and breast cancer incidence and mortality. Over an 11-year follow-up period, 2670 new cases were diagnosed, most of which were ER-positive. While living closer to these facilities was associated with a higher risk of developing breast cancer, many participants also presented additional risk factors, such as a higher BMI and smoking habits. Nonetheless, breast cancer risk decreased proportionately to increased distance from the industrial facilities, likely due to the relatively short

half-life of certain dioxins (Rhee et al., 2023).

Dioxins, particularly TCDD, induce metabolic reprogramming via AhR activation. In murine models, chronic TCDD exposure disrupts one-carbon metabolism and alters key metabolites such as S-adenosylmethionine and S-adenosylhomocysteine during the progression from hepatic steatosis to steatohepatitis (Fling et al., 2020). Consistently, TCDD exposure also disrupts acetyl-CoA metabolism, reducing hepatic acetyl-CoA and β -hydroxybutyrate levels and altering protein acetylation through AhR-mediated mechanisms (Cholico et al., 2023). In human subjects, serum metabolomic profiling revealed that high environmental dioxin levels are associated with disturbances in multiple key metabolic pathways—including fatty acid β -oxidation, essential fatty acid, glycerophospholipid, sphingolipid, arachidonic acid, and purine metabolism—pointing to systemic metabolic dysregulation in response to dioxin exposure (Liang et al., 2020). In human breast cancer cell lines MCF-7 and MDA-MB-231, TCDD upregulates the amino acid transporter LAT1 through AhR activation, involving direct AhR binding to the LAT1 promoter region and increased histone H3 acetylation, which enhances leucine uptake and promotes cancer cell proliferation (Tomblin et al., 2016). Beyond metabolic disruption, TCDD also induces epigenetic alterations (Patrizi and Siciliani de Cumis, 2018). AhR-activating dioxins also remodel chromatin at breast-cancer-relevant loci. In MCF-7 cells, TCDD recruits AhR together with acetylated histone H4 to the COX-2 promoter, enhancing expression via promoter-associated chromatin changes (Degner et al., 2009). Moreover, TCDD drives BRCA1 promoter hypermethylation and epigenetic silencing through AhR-dependent recruitment of DNMT1/MBD2 and histone-modifying enzymes (Papoutsis et al., 2012, 2010).

In an *in vitro* study, Koual et al. (2021) studied how breast cancer MCF-7 cells, in co-culture with hMADS preadipocytes, responded to TCDD exposure in their microenvironment. The TCDD-exposed cells presented reduced adhesion, enhanced expression of ALDH1A3, CYP1A1 and CYP1B1, lower mRNA expression of E-cadherin, and significant morphological alterations, including extended lamellipodia (cytoskeletal projections on the edges of a cell) and giant multinucleated cells. Taken together, these modifications made up a pro-metastatic phenotype. Interestingly, when the same conditions were replicated in zebrafish xenograft models, the number of brain metastases in the TCDD-exposed groups was significantly higher than in the control group (Koual et al., 2021).

In an elegant review, Sweeney et al. (2022) explored the link between dioxins and AhR, a ligand-activated transcription factor that regulates multiple target genes. When activated by dioxins or other pollutants, AhR plays a critical role in breast cancer progression, immune tolerance, tumor microenvironment remodeling, and other alterations that drive chemoresistance and metastasis. Specifically, AhR activation induces the nuclear factor-kappa B (NF- κ B) pathway, which promotes the expression of pro-inflammatory chemokines like interleukin-8 (IL-8). It also regulates chemokine ligand 1 (CXCL1), chemokine ligand 2 (CXCL2), and chemokine ligand 5 (CCL5), which promote cellular migration and macrophage recruitment to the tumor microenvironment. Additionally, AhR activation increases AREG production, leading to tumor proliferation and macrophage infiltration (Sweeney et al., 2022).

Shan et al. (2020) further investigated the effects of mixed exposure to EDCs on human breast cancer cells. MCF-7 cells were exposed to either TCDD, mono-2-ethylhexyl phthalate (MEHP) or both. When the cells were exposed to a single EDC, they showed increased CYP1A1 levels and greater cell migration and invasion. In contrast, exposure to both EDCs was associated with lower CYP1A1 levels and reduced cell migration and invasion. In addition, AhR expression decreased in BALB/c nude mice exposed to both EDCs. These results suggest a competitive antagonism between TCDD and MEHP in their inhibition of MCF-7 cells (Shan et al., 2020).

3. Conclusions and future perspectives

The impact of EDCs on human health, particularly on the development and progression of cancer, has been in the spotlight for many decades. Although research is ongoing, it remains insufficient to bridge the existing gaps in our knowledge, especially given the increasing severity of the issue and the continued exposure to EDCs in daily life. The present review has examined several types of EDCs with the aim of gaining a better understanding of their role in breast cancer and of assessing the extent of our current knowledge. Here we summarize the key effects of these EDCs on breast cancer, discuss the limitations of current research, highlight the important effect of EDC exposure on public health, and examine current and proposed measures to prevent exposure and mitigate the effects thereof.

EDCs influence breast cancer development and progression through multiple mechanisms. They can mimic endogenous ligands and interfere with molecular pathways, primarily estrogen and androgen signaling, which disrupts cellular homeostasis. Additionally, they induce epigenetic modifications, such as altered DNA methylation and histone modifications, which affect gene expression and genomic stability. EDCs can also enhance cell cycle activity, metabolic reprogramming, and resistance to apoptosis. Many EDCs can contribute to increased migration and invasion of other tissues, facilitating metastasis by altering the cytoskeletal structure and modifying the expression of adhesion proteins. Finally, EDCs modulate the tumor microenvironment by promoting chronic inflammation and suppressing the immune system's protective role, thus creating conditions for cancer cells to expand and proliferate more easily (Koual et al., 2020; Liu et al., 2023; Morgan et al., 2017; Wan et al., 2022). Importantly, a central unifying mechanism underlying these effects is the cross-talk between ER and AhR signaling, which integrates estrogenic responses with immune evasion, epigenetic remodeling, and metabolic adaptation, thereby amplifying the oncogenic potential of environmental exposures (Miret et al., 2023; Safe et al., 2013).

Although EDCs were first identified in the 1990s, when several researchers began noticing changes in the wellbeing of humans and other forms of life (Colborn et al., 1993), policies aimed at mitigating their effect remain insufficient (Gore et al., 2015). While EDCs are not yet fully understood and further research is needed to fully comprehend their toxicity, it is clear that some key factors influence EDC exposure, including industrial pollution and certain types of food containers (Fiedler, 1996). For instance, research has shown that living within 10 km of municipal waste incinerators or constant exposure to polluted air from industrial facilities can have an impact on the development and progression of breast cancer (VoPham et al., 2020). These persistent pollutants pose serious health risks, including hormonal disruption and increased cancer risk. In addition, people who consume larger amounts of canned or plastic-wrapped foods face an increased risk of developing breast cancer due to exposure to the EDCs present in these materials (Stillwater et al., 2020). Importantly, these two risk factors have been found to strongly correlate with an individual's socioeconomic status. Furthermore, they could be assessed and controlled through government restrictions and policies (Kassotis et al., 2020).

Taken together, these findings highlight the need for more restrictive laws that limit EDC emission and measures to prevent further exposure of the population to specific EDCs (Kassotis et al., 2020). In this line, the regulation of bisphenols has undergone significant changes recently. On January 3rd, 2025, the European Commission approved a new regulation, which took effect on January 20th. This regulation bans the production of all products containing BPA and its potentially harmful derivatives in materials intended for contact with food and beverages. However, products which are already on the market will remain available until January 2029 (<https://eur-lex.europa.eu/eli/reg/2024/3190/oj/eng>). Exceptions will apply when no suitable microbiologically safe alternative is available. Despite these regulatory efforts, it is important to note that the health effects of these EDCs may well be

present in individuals long after the ban takes effect. However, these measures will help protect younger and future generations.

The European Commission has published multiple recommendations on the acceptable levels of EDCs in food. These limits vary depending on the type of food but are always based on the ALARA (As Low As Reasonably Achievable) principle, as stated in Regulation (UE) 2023/915 (<https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32023R0915>). However, there is only one limit on the level of PCBs and dioxins released from waste incineration facilities: 0.1 ng/Nm³, which applies to the total amount released.

In contrast, the regulations that limit the concentration of parabens in cosmetic products establish a maximum concentration of 0.4 % for the individual short-chain parabens MP and EP and a maximum concentration of 0.8 % for the combination of these parabens. The limit for the long-chain parabens PP and BP is stricter, with a maximum concentration of 0.14 %. Moreover, the European Commission banned the use of several parabens in cosmetic products in 2014 because of their detrimental effects on human health (https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.107.01.0005.01.ENG).

Here we have focused on four of the main EDCs, but individuals can be exposed to thousands of EDCs daily. For the most part, their effects on human health remain unknown, not only in relation to breast cancer but also to other pathologies. Furthermore, new EDCs continue to be identified. For instance, in February 2025, the French Agency for Food, Environment and Occupational Health and Safety proposed that resorcinol, a phenolic compound widely used in the cosmetic, pharmaceutical, and industrial sectors, should be classified as a potential EDC (<https://www.anses.fr/en/content/anses-proposes-classifying-resorcinol-en-docrine-disruptor-european-clp-regulation>). It is clear that safer alternatives must be developed to replace these compounds, as even those with low endocrine-disrupting activity contribute to cumulative exposure, which may still pose health risks. Furthermore, in circumstances where it is impossible to completely avoid exposure to these compounds, efforts should focus on protecting both workers regularly exposed to these chemicals and people living near the sources.

This review has several limitations. One of the primary challenges is the complexity of the mechanisms underlying breast cancer development. Multiple biological pathways interact, making it difficult to isolate the specific role of a single EDC. In addition, we have focused on the disruptive activities of the four EDCs when administered either alone or in combination with only one additional toxic compound. However, humans are simultaneously exposed to numerous EDCs that may interact in a competitive, synergistic, or unpredictable way. Similarly, many of the studies conducted to date have been based on cell models and typically analyzed one or two EDCs at a time. Future research should focus on studying combinations of EDCs, preferably *in vivo*, as such studies have shown greater reliability and informative value. Moreover, epidemiological studies could provide data on the correlation between exposure to a single EDC and the incidence of breast cancer in a specific population, highlighting the need for more studies of this kind. Finally, another important limitation of this review is that many of the available publications, particularly those on PCBs, were outdated, raising the concern that scientific interest in finding solutions to the problem of EDC exposure has declined over time despite their continued widespread presence in daily life.

In conclusion, this study highlights the significant role of bisphenols, PCBs, parabens, and dioxins in the development and progression of breast cancer. BPA promotes cell proliferation, migration, epigenetic alterations, tumor microenvironment modifications, and immunosuppression. PCBs disrupt gene expression and cellular metabolism, although their association with breast cancer risk remains inconclusive. Parabens exhibit estrogenic activity, contributing to cell proliferation and oxidative stress. Dioxins, classified as Group I carcinogens, promote inflammation, metastasis, and treatment resistance, and epidemiological studies suggest that high exposure levels, influenced by environmental factors, diet, and cosmetic use, may increase breast cancer risk.

Given the widespread presence of these EDCs in the environment and their persistence in human adipose tissue, further research is crucial. Importantly, stronger regulations and preventive measures are needed to minimize exposure and mitigate potential health risks. Furthermore, governments need to support more public programs that address environmental and health issues, disseminating this information in schools, clubs, cities, and factories to inform people how to protect themselves and prevent these diseases.

Abbreviations

AhR, aryl hydrocarbon receptor; AP-1, Activator protein 1; AREG, Amphiregulin; BCL2, B-cell lymphoma 2; BMI, Body Mass Index; BPA, Bisphenol A; BPAF, Bisphenol AF; BPF, Bisphenol F; BPS, Bisphenol S; BRCA1, Breast cancer type 1; BRCA2, Breast cancer type 2; CAT, Catalase; CAAs, Cancer-associated adipocytes; CCL28, C-C motif chemokine ligand 28; CCL5, Chemokine ligand 5; CXCL1, Chemokine ligand 1; CXCL12, C-X-C motif chemokine ligand 12; CXCL2, Chemokine ligand 2; CYP1A1, Cytochrome P450 1A1; DNMT1, DNA methyltransferase 1; E1, Estrone; E2, 17 β -estradiol; E3, Estriol; E4, Estetrol; EDC, Endocrine disrupting chemical; EGFR, epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; ER, Estrogen receptor; ER-, Estrogen receptor-negative; ER+, Estrogen receptor-positive; EREs, Estrogen response elements; ESR1, Estrogen receptor 1; FOXM1, Forkhead box M1; GLUT1, Glucose transporter 1; GREB1, Growth regulation by estrogen in breast cancer HBECS, Primary benign breast epithelial cells; HER2, Human epidermal growth factor 2; IGF-1, Insulin like growth factor 1; IL1A, Interleukin 1 alpha; IL1B, Interleukin 1 beta; MAPK/ERK, Mitogen-activated protein kinases and extracellular signal-regulated kinases pathway; MEHP, Mono-2-ethylhexyl phthalate; MMP7, Matrix metalloproteinase 7; MYC, V-myc avian myelocytomatosis viral oncogene homolog; NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; OPFRs, organophosphate flame retardants; p53, Tumor suppressor protein p53; PCBs, Polychlorinated biphenyls; PFAS, Polyfluorinated Alkyl substances; PI3K, Phosphatidylinositol-3-kinase; PI3K/AKT, Phosphatidylinositol-3-kinase and Akt protein pathway; PKA, Protein kinase A; PKC, Protein kinase C; PR, Progesterone receptor; PTEN, Phosphatase and tensin homolog; pRb, Retinoblastoma protein; ROS, Reactive oxygen species; SNPs, Single nucleotide polymorphisms; SOD, Superoxide dismutase; Sp1, Specificity protein 1; TCDD, 2,3,7,8-Tetrachlorodibenzo-p-dioxin; TEF, Toxic equivalency factor; TNBC, Triple negative breast cancer; Tregs, Regulatory T cells.

CRedit authorship contribution statement

Vicenç Ruiz de Porras: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marina Sánchez-Ocaña:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT 4o in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

References

- Al-Thoubaity, F.K., 2020. Molecular classification of breast cancer: a retrospective cohort study. *Ann. Med. Surg.* 49, 44–48.
- Amadou, A., Praud, D., Coudon, T., Deygas, F., Grassot, L., Faure, E., Couvidat, F., Caudeville, J., Bessagnet, B., Salizzoni, P., Gulliver, J., Leffondre, K., Severi, G., Mancini, F.R., Fervers, B., 2021. Risk of breast cancer associated with long-term exposure to benzo[a]pyrene (BaP) air pollution: evidence from the French E3N cohort study. *Environ. Int.* 149, 106399.
- Arnold, M., Morgan, E., Rumgay, H., Mafra, A., Singh, D., Laversanne, M., Vignat, J., Grawal, J.R., Cardoso, F., Siesling, S., Soerjomataram, I., 2022. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast* 66, 15–23.
- Awada, Z., Nasr, R., Akika, R., Cahais, V., Cuenin, C., Zhivagui, M., Herceg, Z., Ghantous, A., Zgheib, N.K., 2019. DNA methylome-wide alterations associated with estrogen receptor-dependent effects of bisphenols in breast cancer. *Clin. Epigenetics* 11, 138.
- Bereketoglu, C., Pradhan, A., 2019. Comparative transcriptional analysis of methylparaben and propylparaben in zebrafish. *Sci. Total Environ.* 671, 129–139.
- Bhan, A., Hussain, I., Ansari, K.I., Bobzean, S.A., Perrotti, L.I., Mandal, S.S., 2014. Bisphenol-A and diethylstilbestrol exposure induces the expression of breast cancer associated long noncoding RNA HOTAIR in vitro and in vivo. *J. Steroid Biochem. Mol. Biol.* 141, 160–170.
- Boberg, J., Taxvig, C., Christiansen, S., Hass, U., 2010. Possible endocrine disrupting effects of parabens and their metabolites. *Reprod. Toxicol.* 30, 301–312.
- Boszkiewicz, K., Sawicka, E., Piwowar, A., 2020. The impact of xenoestrogens on effectiveness of treatment for hormone-dependent breast cancer - current state of knowledge and perspectives for research. *Ann. Agric. Environ. Med.* 27, 526–534.
- Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I., Jemal, A., 2022. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 74, 229–263.
- Caporale, N., Leemans, M., Birgersson, L., Germain, P.L., Cheroni, C., Borbely, G., Engdahl, E., Lindh, C., Bressan, R.B., Cavallo, F., Chorev, N.E., D'Agostino, G.A., Pollard, S.M., Rigoli, M.T., Tenderini, E., Tobon, A.L., Trattaro, S., Troglia, F., Zanella, M., Bergman, A., Damdimopoulou, P., Jonsson, M., Kiess, W., Kitraki, E., Kiviranta, H., Nanberg, E., Ober, M., Rantakokko, P., Ruden, C., Soder, O., Bornehag, C.G., Demeneix, B., Fini, J.B., Gennings, C., Ruegg, J., Sturve, J., Testa, G., 2022. From cohorts to molecules: adverse impacts of endocrine disrupting mixtures. *Science* 375, eabe8244.
- Carpenter, D.O., 2006. Polychlorinated biphenyls (PCBs): routes of exposure and effects on human health. *Rev. Environ. Health* 21, 1–23.
- Chatterjee, S., Adhikary, S., Bhattacharya, S., Chakraborty, A., Dutta, S., Roy, D., Ganguly, A., Nanda, S., Rajak, P., 2024. Parabens as the double-edged sword: understanding the benefits and potential health risks. *Sci. Total Environ.* 954, 176547.
- Chen, P., Li, B., Ou-Yang, L., 2022. Role of estrogen receptors in health and disease. *Front. Endocrinol. (Lausanne)* 13, 839005.
- Cholico, G.N., Orłowska, K., Fling, R.R., Sink, W.J., Zacharewski, N.A., Fader, K.A., Nault, R., Zacharewski, T., 2023. Consequences of reprogramming acetyl-CoA metabolism by 2,3,7,8-tetrachlorodibenzo-p-dioxin in the mouse liver. *Sci. Rep.* 13, 4138.
- Colborn, T., vom Saal, F.S., Soto, A.M., 1993. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. *Environ. Health Perspect.* 101, 378–384.
- Curtis, S.W., Cobb, D.O., Kilaru, V., Terrell, M.L., Kennedy, E.M., Marder, M.E., Barr, D. B., Marsit, C.J., Marcus, M., Conneely, K.N., Smith, A.K., 2019. Exposure to polybrominated biphenyl (PBB) associates with genome-wide DNA methylation differences in peripheral blood. *Epigenetics* 14, 52–66.
- Dairkee, S.H., Moore, D.H., Luciani, M.G., Anderle, N., Gerona, R., Ky, K., Torres, S.M., Marshall, P.V., Goodson III, W.H., 2023. Reduction of daily-use parabens and phthalates reverses accumulation of cancer-associated phenotypes within disease-free breast tissue of study subjects. *Chemosphere* 322, 138014.
- Daly, A.A., Rolph, R., Cutress, R.I., Copson, E.R., 2021. A review of modifiable risk factors in young women for the prevention of breast cancer. *Breast Cancer (Dove Med Press)* 13, 241–257.
- Degner, S.C., Papoutsis, A.J., Selmin, O., Romagnolo, D.F., 2009. Targeting of aryl hydrocarbon receptor-mediated activation of cyclooxygenase-2 expression by the indole-3-carbinol metabolite 3,3'-diindolylmethane in breast cancer cells. *J. Nutr.* 139, 26–32.
- Del Favero, G., Bergen, J., Palm, L., Fellingner, C., Matlaeva, M., Szabadi, A., Fernandes, A.S., Saraiva, N., Schroder, C., Marko, D., 2024. Short-Term exposure to foodborne xenoestrogens affects breast cancer cell morphology and motility relevant for metastatic behavior in vitro. *Chem. Res. Toxicol.* 37, 1634–1650.
- Denison, M.S., Nagy, S.R., 2003. Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu. Rev. Pharm. Toxicol.* 43, 309–334.
- Desnavaillès, P., Praud, D., Le Provost, B., Kobayashi, H., Deygas, F., Amadou, A., Coudon, T., Grassot, L., Faure, E., Couvidat, F., Severi, G., Mancini, F.R., Fervers, B., Proust-Lima, C., Leffondre, K., 2024. Trajectories of long-term exposure to PCB153 and benzo[a]pyrene (BaP) air pollution and risk of breast cancer. *Environ. Health* 23, 72.
- DeVito, M., Bokkers, B., van Duursen, M.B.M., van Ede, K., Feeley, M., Antunes Fernandes Gaspar, E., Haws, L., Kennedy, S., Peterson, R.E., Hoogenboom, R., Nohara, K., Petersen, K., Rider, C., Rose, M., Safe, S., Schrenk, D., Wheeler, M.W., Wikoff, D.S., Zhao, B., van den Berg, M., 2024. The 2022 world health organization reevaluation of human and mammalian toxic equivalency factors for polychlorinated dioxins, dibenzofurans and biphenyls. *Regul. Toxicol. Pharm.* 146, 105525.
- Deygas, F., Amadou, A., Coudon, T., Grassot, L., Couvidat, F., Bessagnet, B., Faure, E., Salizzoni, P., Gulliver, J., Caudeville, J., Severi, G., Mancini, F.R., Leffondre, K., Fervers, B., Praud, D., 2021. Long-term atmospheric exposure to PCB153 and breast cancer risk in a case-control study nested in the French E3N cohort from 1990 to 2011. *Environ. Res.* 195, 110743.
- Doherty, L.F., Bromer, J.G., Zhou, Y., Aldad, T.S., Taylor, H.S., 2010. In utero exposure to diethylstilbestrol (DES) or bisphenol-A (BPA) increases EZH2 expression in the mammary gland: an epigenetic mechanism linking endocrine disruptors to breast cancer. *Horm. Cancer* 1, 146–155.
- Dong, Z., He, L., Wu, J., Xie, C., Geng, S., Wu, J., Zhong, C., Li, X., 2025. Bisphenol A-induced cancer-associated adipocytes promotes breast carcinogenesis via CXCL12/AKT signaling. *Mol. Cell Endocrinol.* 599, 112473.
- Donini, C.F., El Helou, M., Wierinckx, A., Gyorffy, B., Aires, S., Escande, A., Croze, S., Clezardin, P., Lachuer, J., Diab-Assaf, M., Ghayad, S.E., Fervers, B., Cavailles, V., Maguer-Satta, V., Cohen, P.A., 2020. Long-Term exposure of Early-Transformed human mammary cells to low doses of Benzo[a]pyrene and/or bisphenol A enhances their cancerous phenotype via an AhR/GPR30 interplay. *Front. Oncol.* 10, 712.
- Elshehly, W.M., Mourad, G.M., Mehanna, R.A., Kholief, M.A., El-Nikhely, N.A., Awaad, A. K., Attia, M.H., 2022. The potential implications of estrogenic and antioxidant-dependent activities of high doses of methyl paraben on MCF7 breast cancer cells. *J. Biochem. Mol. Toxicol.* 36, e23012.
- Fernandez, M.F., Kiviranta, H., Molina-Molina, J.M., Laine, O., Lopez-Espinosa, M.J., Vartiainen, T., Olea, N., 2008. Polychlorinated biphenyls (PCBs) and hydroxy-PCBs in adipose tissue of women in southeast Spain. *Chemosphere* 71, 1196–1205.
- Fiedler, H., 1996. Sources of PCDD/PCDF and impact on the environment. *Chemosphere* 32, 55–64.
- Fiolet, T., Casagrande, C., Nicolas, G., Horvath, Z., Frenoy, P., Weiderpass, E., Katzke, V., Kaaks, R., Rodriguez-Barranco, M., Panico, S., Sacerdote, C., Manjer, J., Sonestedt, E., Grióni, S., Agudo, A., Rylander, C., Haugdahl Nost, T., Skeie, G., Tjonneland, A., Raaschou-Nielsen, O., Ardanaz, E., Amiano, P., Dolores Chirlaque Lopez, M., Schulze, M.B., Wennberg, M., Harlid, S., Cairat, M., Kvaskoff, M., Huybrechts, I., Romana Mancini, F., 2022. Dietary intakes of dioxins and polychlorobiphenyls (PCBs) and breast cancer risk in 9 European countries. *Environ. Int.* 163, 107213.
- Fling, R.R., Doskey, C.M., Fader, K.A., Nault, R., Zacharewski, T.R., 2020. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) dysregulates hepatic one carbon metabolism during the progression of steatosis to steatohepatitis with fibrosis in mice. *Sci. Rep.* 10, 14831.
- Focaccetti, C., Nardozi, D., Benvenuto, M., Lucarini, V., Angiolini, V., Carrano, R., Scimeca, M., Servadei, F., Mauriello, A., Mancini, P., Besharat, Z.M., Milella, M., Migliaccio, S., Ferretti, E., Cifaldi, L., Masuelli, L., Palumbo, C., Bei, R., 2024. Bisphenol-A in drinking water accelerates mammary cancerogenesis and favors an immunosuppressive tumor microenvironment in BALB-neuT mice. *Int. J. Mol. Sci.* 25.
- Fuentes, N., Silveyra, P., 2019. Estrogen receptor signaling mechanisms. *Adv. Protein Chem. Struct. Biol.* 116, 135–170.
- Goodman, S., Chappell, G., Guyton, K.Z., Pogribny, I.P., Rusyn, I., 2022. Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: an update of a systematic literature review. *Mutat. Res. Rev. Mutat. Res.* 789, 108408.
- Gore, A.C., Chappell, V.A., Fenton, S.E., Flaws, J.A., Nadal, A., Prins, G.S., Toppari, J., Zoeller, R.T., 2015. EDC-2: the endocrine society's second scientific statement on Endocrine-Disrupting chemicals. *Endocr. Rev.* 36, E1–E150.
- Guzel Bayulkun, D., Ayaz Tuylu, B., 2019. In vitro genotoxic and cytotoxic effects of some paraben esters on human peripheral lymphocytes. *Drug Chem. Toxicol.* 42, 386–393.
- Hager, E., Chen, J., Zhao, L., 2022. Minireview: parabens exposure and breast cancer. *Int. J. Environ. Res. Public Health* 19.
- Harbeck, N., Penault-Llorca, F., Cortes, J., Gnant, M., Houssami, N., Poortmans, P., Ruddy, K., Tsang, J., Cardoso, F., 2019. Breast cancer. *Nat. Rev. Dis. Prim.* 5, 66.
- Hirao-Suzuki, M., 2021. Estrogen receptor beta as a possible Double-Edged sword molecule in breast cancer: a mechanism of alteration of its role by exposure to Endocrine-Disrupting chemicals. *Biol. Pharm. Bull.* 44, 1594–1597.
- Ho, V., Pelland-St-Pierre, L., Gravel, S., Bouchard, M.F., Verner, M.A., Labreche, F., 2022. Endocrine disruptors: challenges and future directions in epidemiologic research.

- Environ. Res 204, 111969. (<https://www.who.int/publications/i/item/state-of-the-science-of-endocrine-disrupting-chemicals>).
- Ishfaq, A., Nasrullah, M.A., Khan, J.S., Malik, S., Tareen, U., Anees, M., Sultan, A., Murtaza, I., 2023. A cohort study investigating the role of bisphenol A in the molecular pathogenesis of breast cancer. *J. Cancer Res. Clin. Oncol.* 149, 14565–14575.
- Kassotis, C.D., Vandenberg, L.N., Demeneix, B.A., Porta, M., Slama, R., Trasande, L., 2020. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. *Lancet Diabetes Endocrinol.* 8, 719–730.
- Keshavarz-Maleki, R., Kaviani, A., Omranipour, R., Gholami, M., Khoshayand, M.R., Ostad, S.N., Sabzevari, O., 2021. Bisphenol-A in biological samples of breast cancer mastectomy and mammoplasty patients and correlation with levels measured in urine and tissue. *Sci. Rep.* 11, 18411.
- Kim, J.Y., Choi, H.G., Lee, H.M., Lee, G.A., Hwang, K.A., Choi, K.C., 2017. Effects of bisphenol compounds on the growth and epithelial mesenchymal transition of MCF-7 CV human breast cancer cells. *J. Biomed. Res.* 31, 358–369.
- Kortenkamp, A., 2007. Ten years of mixing cocktails: a review of combination effects of endocrine-disrupting chemicals. *Environ. Health Perspect.* 115 (1), 98–105.
- Koual, M., Tomkiewicz, C., Cano-Sancho, G., Antignac, J.P., Bats, A.S., Coumoul, X., 2020. Environmental chemicals, breast cancer progression and drug resistance. *Environ. Health* 19, 117.
- Koual, M., Tomkiewicz, C., Guerrero, I.C., Sherr, D., Barouki, R., Coumoul, X., 2021. Aggressiveness and metastatic potential of breast cancer cells Co-Cultured with preadipocytes and exposed to an environmental pollutant dioxin: an in vitro and in vivo zebrafish study. *Environ. Health Perspect.* 129, 37002.
- Kwon, Y., 2022. Potential Pro-Tumorigenic effect of bisphenol A in breast cancer via altering the tumor microenvironment. *Cancers* 14.
- Leng, L., Li, J., Luo, X.M., Kim, J.Y., Li, Y.M., Guo, X.M., Chen, X., Yang, Q.Y., Li, G., Tang, N.J., 2016. Polychlorinated biphenyls and breast cancer: a congener-specific meta-analysis. *Environ. Int.* 88, 133–141.
- Li, Y., Zheng, N., Sun, S., Wang, S., Li, X., Pan, J., Li, M., Lang, L., Yue, Z., Zhou, B., 2023. Exposure estimates of parabens from personal care products compared with biomonitoring data in human hair from northeast China. *Ecotoxicol. Environ. Saf.* 267, 115635.
- Liang, Y., Tang, Z., Jiang, Y., Ai, C., Peng, J., Liu, Y., Chen, J., Zhang, J., Cai, Z., 2020. Serum metabolic changes associated with dioxin exposure in a Chinese Male cohort. *Environ. Int.* 143, 105984.
- Liu, H., Sun, Y., Ran, L., Li, J., Shi, Y., Mu, C., Hao, C., 2023. Endocrine-disrupting chemicals and breast cancer: a meta-analysis. *Front. Oncol.* 13, 1282651.
- Lloyd, V., Morse, M., Purakal, B., Parker, J., Benard, P., Crone, M., Pfiffner, S., Szymd, M., Dinda, S., 2019. Hormone-Like effects of bisphenol A on p53 and estrogen receptor alpha in breast cancer cells. *Biores Open Access* 8, 169–184.
- Mandal, P.K., 2005. Dioxin: a review of its environmental effects and its aryl hydrocarbon receptor biology. *J. Comp. Physiol. B* 175, 221–230.
- Miret, N.V., Pontillo, C.A., Bujan, S., Chiappini, F.A., Randi, A.S., 2023. Mechanisms of breast cancer progression induced by environment-polluting aryl hydrocarbon receptor agonists. *Biochem. Pharm.* 216, 115773.
- Moreman, J., Lee, O., Trznadel, M., David, A., Kudoh, T., Tyler, C.R., 2017. Acute toxicity, teratogenic, and estrogenic effects of bisphenol A and its alternative replacements bisphenol S, bisphenol F, and bisphenol AF in zebrafish Embryo-Larvae. *Environ. Sci. Technol.* 51, 12796–12805.
- Morgan, M., Deoraj, A., Felty, Q., Roy, D., 2017. Environmental estrogen-like endocrine disrupting chemicals and breast cancer. *Mol. Cell Endocrinol.* 457, 89–102.
- Morin, S.M., Majhi, P.D., Crisi, G.M., Gregory, K.J., Franca, R., Schaub, B., Mason, H., Casaubon, J.T., Cao, Q.J., Haddad, S., Makari-Judson, G., Jerry, D.J., Schneider, S.S., 2022. Interindividual variation contributes to differential PCB 126 induced gene expression in primary breast epithelial cells and tissues. *Ecotoxicol. Environ. Saf.* 241, 113722.
- Nilsson, S., Makela, S., Treuter, E., Tujague, M., Thomsen, J., Andersson, G., Enmark, E., Pettersson, K., Warner, M., Gustafsson, J.A., 2001. Mechanisms of estrogen action. *Physiol. Rev.* 81, 1535–1565.
- Nowak, K., Ratajczak-Wrona, W., Gorska, M., Jablonska, E., 2018. Parabens and their effects on the endocrine system. *Mol. Cell Endocrinol.* 474, 238–251.
- Nowak, K., Jablonska, E., Ratajczak-Wrona, W., 2019. Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells. *Environ. Int.* 125, 350–364.
- Obringer, C., Wu, S., Troutman, J., Karb, M., Lester, C., 2021. Effect of chain length and branching on the in vitro metabolism of a series of parabens in human liver S9, human skin S9, and human plasma. *Regul. Toxicol. Pharm.* 122, 104918.
- Onozuka, D., Nakamura, Y., Tsuji, G., Furue, M., 2020. Mortality in yusho patients exposed to polychlorinated biphenyls and polychlorinated dibenzofurans: a 50-year retrospective cohort study. *Environ. Health* 19, 119.
- Papoutsis, A.J., Lamore, S.D., Wondrak, G.T., Selmin, O.I., Romagnolo, D.F., 2010. Resveratrol prevents epigenetic silencing of BRCA-1 by the aromatic hydrocarbon receptor in human breast cancer cells. *J. Nutr.* 140, 1607–1614.
- Papoutsis, A.J., Borg, J.L., Selmin, O.I., Romagnolo, D.F., 2012. BRCA-1 promoter hypermethylation and silencing induced by the aromatic hydrocarbon receptor-ligand TCDD are prevented by resveratrol in MCF-7 cells. *J. Nutr. Biochem.* 23, 1324–1332.
- Parada Jr., H., Sun, X., Tse, C.K., Engel, L.S., Hoh, E., Olshan, A.F., Troester, M.A., 2020. Plasma levels of polychlorinated biphenyls (PCBs) and breast cancer mortality: the carolina breast cancer study. *Int. J. Hyg. Environ. Health* 227, 113522.
- Parada Jr., H., Sahrai, L., Wolff, M.S., Santella, R.M., Chen, J., Neugut, A.I., Teitelbaum, S.L., 2022. Urinary parabens and breast cancer risk: modification by LINE-1 and LUMA global DNA methylation, and associations with breast cancer defined by tumor promoter methylation status. *Mol. Carcinog.* 61, 1002–1015.
- Park, N.Y., Cho, Y.H., Choi, K., Lee, E.H., Kim, Y.J., Kim, J.H., Kho, Y., 2019. Parabens in breast milk and possible sources of exposure among lactating women in Korea. *Environ. Pollut.* 255, 113142.
- Patrizi, B., Siciliani de Cumis, M., 2018. TCDD toxicity mediated by epigenetic mechanisms. *Int. J. Mol. Sci.* 19.
- Puga, A., Ma, C., Marlowe, J.L., 2009. The aryl hydrocarbon receptor cross-talks with multiple signal transduction pathways. *Biochem. Pharm.* 77, 713–722.
- Qin, Q., Yang, B., Liu, J., Song, E., Song, Y., 2022. Polychlorinated biphenyl quinone exposure promotes breast cancer aerobic glycolysis: an in vitro and in vivo examination. *J. Hazard Mater.* 424, 127512.
- Reeves, K.W., Schneider, S., Xue, J., Kannan, K., Mason, H., Johnson, M., Makari-Judson, G., Santana, M.D., 2018. Bisphenol-A in breast adipose tissue of breast cancer cases and controls. *Environ. Res.* 167, 735–738.
- Rhee, J., Medgyesi, D.N., Fisher, J.A., White, A.J., Sampson, J.N., Sandler, D.P., Ward, M. H., Jones, R.R., 2023. Residential proximity to dioxin emissions and risk of breast cancer in the sister study cohort. *Environ. Res.* 222, 115297.
- Rochester, J.R., Bolden, A.L., 2015. Bisphenol s and F: a systematic review and comparison of the hormonal activity of bisphenol A substitutes. *Environ. Health Perspect.* 123, 643–650.
- Safe, S., Lee, S.O., Jin, U.H., 2013. Role of the aryl hydrocarbon receptor in carcinogenesis and potential as a drug target. *Toxicol. Sci.* 135, 1–16.
- Safe, S.H., 1994. Polychlorinated biphenyls (PCBs): environmental impact, biochemical and toxic responses, and implications for risk assessment. *Crit. Rev. Toxicol.* 24, 87–149.
- Shan, A., Leng, L., Li, J., Luo, X.M., Fan, Y.J., Yang, Q., Xie, Q.H., Chen, Y.S., Ni, C.S., Guo, L.M., Tang, H., Chen, X., Tang, N.J., 2020. TCDD-induced antagonism of MEHP-mediated migration and invasion partly involves aryl hydrocarbon receptor in MCF7 breast cancer cells. *J. Hazard Mater.* 398, 122869.
- Shi, Z., Li, Y., Song, X., Wang, Y., Li, J., Wei, S., 2024. The burden of cancer attributable to dietary dioxins and dioxin-like compounds exposure in China, 2000–2020. *Environ. Int.* 194, 109080.
- Singh, D.D., 2024. Epigenetic mechanisms of Endocrine-Disrupting chemicals in breast cancer and their impact on dietary intake. *J. Xenobiot.* 15.
- Stillwater, B.J., Bull, A.C., Romagnolo, D.F., Neumayer, L.A., Donovan, M.G., Selmin, O. I., 2020. Bisphenols and risk of breast cancer: a narrative review of the impact of diet and bioactive food components. *Front. Nutr.* 7, 581388.
- Sweeney, C., Lazennec, G., Vogel, C.F.A., 2022. Environmental exposure and the role of AhR in the tumor microenvironment of breast cancer. *Front. Pharm.* 13, 1095289.
- Terasaki, M., Yasuda, M., Makino, M., Shimoi, K., 2015. Aryl hydrocarbon receptor potency of chlorinated parabens in the aquatic environment. *Environmental Science Water Research Technology* 1, 375–382.
- Tomlin, J.K., Arthur, S., Primerano, D.A., Chaudhry, A.R., Fan, J., Denvir, J., Salisbury, T.B., 2016. Aryl hydrocarbon receptor (AHR) regulation of L-Type amino acid transporter 1 (LAT-1) expression in MCF-7 and MDA-MB-231 breast cancer cells. *Biochem. Pharm.* 106, 94–103.
- Tong, J.H., Elmore, S., Huang, S.S., Tachachartvanich, P., Manz, K., Pennell, K., Wilson, M.D., Borowsky, A., La Merrill, M.A., 2023. Chronic exposure to low levels of parabens increases mammary cancer growth and metastasis in mice. *Endocrinology* 164.
- VoPham, T., Bertrand, K.A., Jones, R.R., Deziel, N.C., DuPre, N.C., James, P., Liu, Y., Vieira, V.M., Tamimi, R.M., Hart, J.E., Ward, M.H., Laden, F., 2020. Dioxin exposure and breast cancer risk in a prospective cohort study. *Environ. Res.* 186, 109516.
- Wan, M.L.Y., Co, V.A., El-Nezami, H., 2022. Endocrine disrupting chemicals and breast cancer: a systematic review of epidemiological studies. *Crit. Rev. Food Sci. Nutr.* 62, 6549–6576.
- Winkler, J., Liu, P., Phong, K., Hinrichs, J.H., Ataii, N., Williams, K., Hadler-Olsen, E., Samson, S., Gartner, Z.J., Fisher, S., Werb, Z., 2022. Bisphenol A replacement chemicals, BPF and BPS, induce protumorigenic changes in human mammary gland organoid morphology and proteome. *Proc. Natl. Acad. Sci. USA* 119, e2115308119.
- Ye, X., Bishop, A.M., Reidy, J.A., Needham, L.L., Calafat, A.M., 2006. Parabens as urinary biomarkers of exposure in humans. *Environ. Health Perspect.* 114, 1843–1846.
- Yersal, O., Barutca, S., 2014. Biological subtypes of breast cancer: prognostic and therapeutic implications. *World J. Clin. Oncol.* 5, 412–424.
- Zani, C., Toninelli, G., Filisetti, B., Donato, F., 2013. Polychlorinated biphenyls and cancer: an epidemiological assessment. *J. Environ. Sci. Health C. Environ. Carcinog. Ecotoxicol. Rev.* 31, 99–144.
- Zhang, J., Huang, Y., Wang, X., Lin, K., Wu, K., 2015. Environmental polychlorinated biphenyl exposure and breast cancer risk: a Meta-Analysis of observational studies. *PLoS One* 10, e0142513.