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REVIEW ARTICLE

Bisphenol A and Breast Cancer: Mechanisms of Carcinogenicity, Tumor Microenvironment Modulation, and Nutritional Interventions

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ABSTRACT: Bisphenol A (BPA) is a synthetic chemical widely used in polycarbonate plastics, epoxy resins, and consumer products, including food containers, thermal papers, and medical devices. Over the past decades, BPA has been identified as an endocrine-disrupting chemical (EDC) due to its structural similarity to 17β-estradiol, enabling it to interfere with hormonal signaling pathways. Accumulating evidence links BPA exposure—even at low, environmentally relevant doses—to adverse health outcomes, including reproductive disorders, metabolic diseases, and hormone-related cancers such as breast cancer. This review synthesizes current research on BPA's carcinogenic potential, focusing on its molecular mechanisms, influence on breast cancer subtypes, and interactions with the tumor microenvironment. BPA exerts its effects through genomic pathways (e.g., estrogen receptor-mediated gene activation) and non-genomic signaling (e.g., GPER, MAPK/ERK, and PI3K/AKT pathways), promoting proliferation, survival, and metastasis. Notably, BPA impacts not only estrogen receptor-positive (ER+) breast cancers but also triple-negative breast cancer (TNBC) through estrogen-independent mechanisms. Furthermore, BPA reprograms cancer-associated fibroblasts (CAFs) and immune cells within the tumor microenvironment, fostering a pro-tumorigenic niche. Emerging evidence suggests that dietary factors can modulate BPA's effects—either exacerbating its toxicity (e.g., high-fat diets, alcohol) or mitigating harm (e.g., phytoestrogens, polyphenols). Given the limitations of current regulatory thresholds, this review underscores the need for revised safety standards, increased public awareness, and interdisciplinary strategies to reduce exposure. Understanding BPA's multifaceted role in breast carcinogenesis is critical for developing preventive and therapeutic interventions.

Keywords: Bisphenol A (BPA), Endocrine disruption, Breast carcinogenesis, Tumor microenvironment, Nutritional modulation, Epigenetic alterations

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1. INTRODUCTION

Bisphenol A (BPA) is a synthetic organic compound that has been widely utilized in the manufacturing of polycarbonate plastics and epoxy resins since its industrial introduction in the 1950s [1]. Its chemical stability, durability, and versatility have led to its incorporation into a vast array of consumer products, including plastic water bottles [2], food storage containers, medical devices, dental sealants, children's toys, and the protective linings of canned foods and beverages. This ubiquity has resulted in near-universal human exposure, with BPA detectable in the urine of over 90% of the general population in industrialized nations. One of the most concerning aspects of BPA is its structural resemblance to 17β-estradiol, the primary endogenous estrogen in humans [3]. This similarity enables BPA to bind to and activate estrogen receptors (ERα and ERβ), as well as other nuclear and membrane-associated receptors, thereby interfering with normal endocrine signaling pathways [4]. As an endocrine-

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disrupting chemical (EDC), BPA can dysregulate hormonal homeostasis, leading to a wide range of adverse health effects, including developmental and reproductive abnormalities, metabolic disorders such as obesity and diabetes, and an increased risk of hormone-dependent cancers, particularly breast and prostate cancer.

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality [5]. While genetic predispositions, such as mutations in BRCA1 and BRCA2, and lifestyle factors, including obesity and alcohol consumption, are well-established contributors to breast cancer risk, mounting evidence implicates environmental endocrine disruptors like BPA as significant modifiable risk factors. Numerous in vitro and in vivo studies have demonstrated that BPA exposure can alter gene expression patterns [6], promote uncontrolled cell proliferation, suppress apoptosis, and induce DNA damage in mammary epithelial cells—hallmarks of carcinogenesis. Perhaps even more alarming is the growing recognition that BPA exerts biological effects at doses far below those currently deemed safe by regulatory agencies. Low-dose exposure, particularly during critical developmental stages such as fetal development, infancy, and puberty, has been shown to predispose mammary tissue to neoplastic transformation later in life through epigenetic modifications and long-lasting alterations in gene expression [7]. These findings challenge the traditional toxicological paradigm that assumes higher doses invariably produce greater effects and highlight the inadequacy of existing regulatory standards in protecting vulnerable populations.

The mechanisms by which BPA contributes to breast cancer are multifaceted and extend beyond its classical estrogen-mimicking properties [8]. In addition to binding nuclear estrogen receptors and modulating the transcription of estrogen-responsive genes, BPA can activate rapid, non-genomic signaling cascades through membrane-associated receptors such as GPER (G protein-coupled estrogen receptor). These pathways, including MAPK/ERK, PI3K/AKT, and JNK, play crucial roles in cell survival, proliferation, and migration, all of which are central to cancer progression [9]. Furthermore, BPA has been shown to disrupt normal mammary gland development, promote the expansion of cancer stem-like cells, and induce epithelial-mesenchymal transition (EMT), a key process in metastasis. Compounding these direct effects on mammary epithelial cells, emerging research indicates that BPA can also remodel the tumor microenvironment by activating cancer-associated fibroblasts (CAFs) and suppressing anti-tumor immune responses, thereby fostering a pro-tumorigenic niche [10].

Adding another layer of complexity, the interplay between BPA exposure and dietary factors can either exacerbate or mitigate its carcinogenic effects. For instance, high-fat diets and alcohol consumption have been shown to enhance BPA's bioavailability and metabolic persistence, whereas bioactive food components such as polyphenols, cruciferous vegetable-derived compounds, and omega-3 fatty acids may counteract its harmful effects through antioxidant, anti-inflammatory, and detoxification-promoting mechanisms. Understanding these interactions is critical for developing evidence-based dietary recommendations to reduce BPA-associated breast cancer risk (Figure 1).

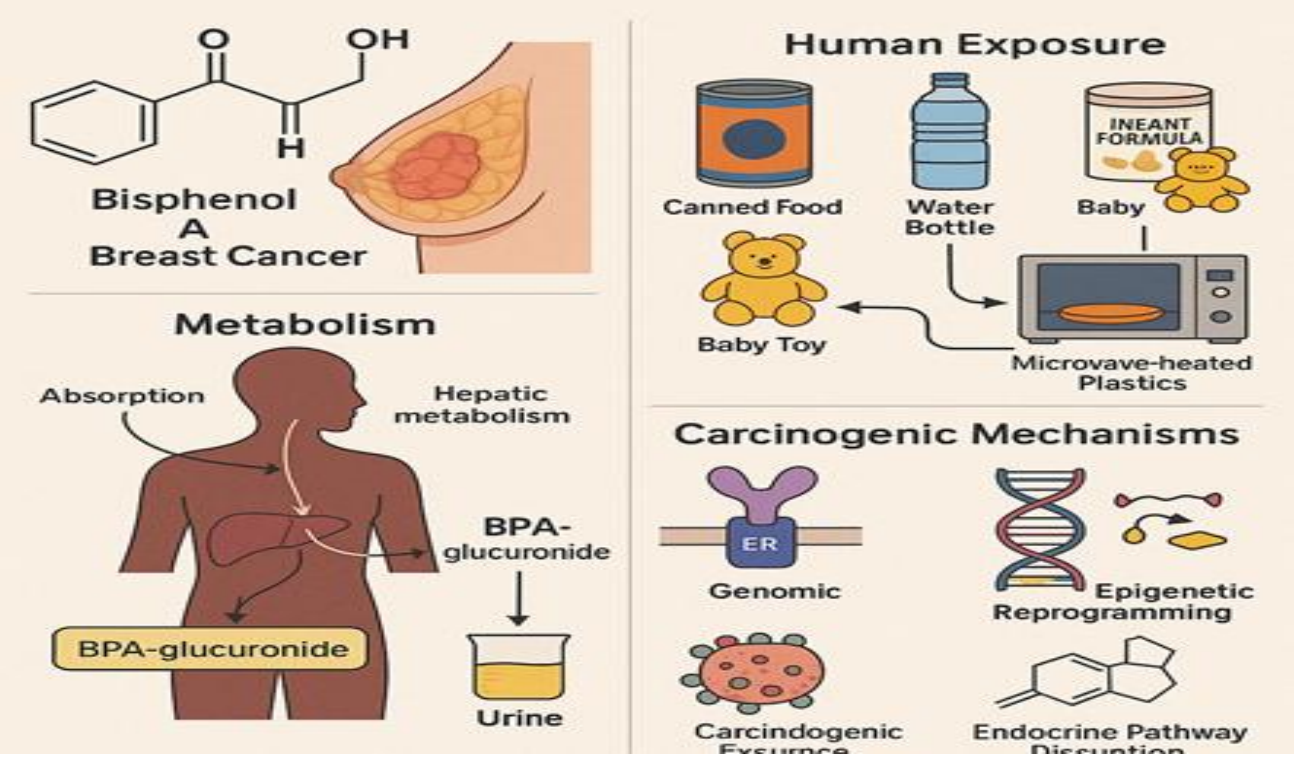

Fig. 1. Pathways of BPA exposure and its potential impacts on human health, emphasizing sources of exposure, metabolic fate, and target tissues relevant to breast carcinogenesis.

This review provides a comprehensive synthesis of current knowledge on BPA's role in breast cancer, with a particular emphasis on three understudied yet critical aspects: (1) the differential impact of BPA across molecular subtypes of breast cancer, including estrogen receptor-positive (ER+), HER2-enriched, and triple-negative breast cancer (TNBC), highlighting its ability to drive malignancy through both hormonal and non-hormonal pathways; (2) the emerging role of BPA in reprogramming the tumor microenvironment, particularly through its activation of CAFs and modulation of immune cell function, which has significant implications for tumor progression and therapy resistance; and (3) the potential for dietary and pharmacological interventions to offset BPA's carcinogenic effects, offering practical strategies for risk reduction. By integrating findings from mechanistic, epidemiological, and translational studies, this review bridges gaps in the current literature and underscores the need for a multidisciplinary approach to address BPA as a preventable environmental carcinogen. Given the pervasive nature of BPA exposure and its potential to contribute to breast cancer development and progression, this review calls for urgent action on multiple fronts. Enhanced regulatory measures, informed by up-to-date scientific evidence, are needed to minimize population-level exposure. Public health initiatives must prioritize education on exposure reduction strategies, particularly for high-risk groups such as pregnant women and young children. Finally, further research is warranted to explore the long-term consequences of BPA exposure, develop biomarkers for early detection of BPA-associated carcinogenesis, and evaluate the efficacy of targeted interventions. Addressing these challenges will require collaboration among researchers, clinicians, policymakers, and the public to mitigate the growing burden of BPA-related breast cancer.

2. HUMAN EXPOSURE AND METABOLISM OF BPA

Human exposure to Bisphenol A (BPA) has become nearly unavoidable in modern society due to its widespread incorporation into consumer products. The primary route of exposure is through oral ingestion, with contaminated food and beverages serving as the major sources. Studies have demonstrated that BPA readily migrates from packaging materials into consumables, particularly under conditions that accelerate chemical leaching, such as exposure to heat, mechanical stress (e.g., scratching), or acidic/alkaline environments [10]. For instance, microwaving food in plastic containers or repeatedly washing them can significantly increase BPA transfer into food, sometimes by several orders of magnitude [11]. This is especially concerning for canned foods and beverages, as their epoxy resin linings—designed to prevent metal corrosion—are a well-documented reservoir of BPA. Research suggests that dietary intake accounts for approximately 90% of total human BPA exposure [12], making it the dominant exposure pathway. Alarmingly, even products marketed as "BPA-free" often contain structurally similar alternatives like bisphenol S (BPS) or bisphenol F (BPF), which may exhibit comparable or even greater endocrine-disrupting potency than BPA itself [13, 14].

In addition to dietary intake, other exposure routes contribute to overall BPA burden. Inhalation of airborne BPA represents a significant exposure pathway, particularly in occupational settings where plastic manufacturing or recycling occurs. The general population may also inhale BPA through household dust containing microplastics or thermal paper particles. Dermal absorption constitutes another important exposure route, especially for cashiers and other workers who frequently handle thermal receipt papers without protective gloves [15]. These receipts often contain substantial quantities of unbound BPA that can be readily absorbed through skin contact, with studies showing detectable increases in urinary BPA levels following handling. The combination of these multiple exposure pathways results in continuous, low-level BPA exposure for most individuals throughout their lifetimes.

Once absorbed, BPA undergoes extensive first-pass metabolism primarily in the liver, where it is converted to less biologically active metabolites. The two major metabolic pathways involve conjugation by UDP-glucuronosyltransferases (UGTs) to form BPA-glucuronide and by sulfotransferases to produce BPA-sulfate [16]. These conjugated metabolites were traditionally considered biologically inert and were thought to be efficiently excreted through urine and bile [17]. However, emerging evidence challenges this assumption, as unconjugated (active) BPA has been detected in various biological matrices, including serum, breast milk, placental tissue, and fetal circulation [18]. These findings suggest that current metabolic pathways may not provide complete protection against BPA's endocrine-disrupting effects. Several factors influence individual metabolic capacity, including age, genetic polymorphisms in detoxification enzymes, liver function, and concurrent exposure to other xenobiotics. Of particular concern are developing fetuses and neonates, whose immature metabolic systems have limited capacity for BPA detoxification, leading to prolonged exposure to the bioactive compound [19]. Similarly, individuals with compromised liver function, such as those with non-alcoholic fatty liver disease or cirrhosis, may exhibit impaired BPA clearance, resulting in higher circulating levels of unconjugated BPA.

The lipophilic nature of BPA further complicates its toxicokinetic profile, as it tends to accumulate in adipose tissue over time [6]. This bioaccumulation is especially relevant for breast tissue, which has a high lipid content and may serve as a long-term reservoir for BPA. Such sequestration creates a persistent source of endogenous exposure, as stored BPA can be gradually released back into circulation, potentially causing prolonged endocrine disruption even after external exposure has ceased [16]. Extensive biomonitoring studies have confirmed the presence of BPA and its metabolites in various human tissues and fluids, including urine, blood, breast milk, amniotic fluid, placental tissue, and adipose tissue [20]. Perhaps most

concerning is the detection of BPA in umbilical cord blood, demonstrating that fetal exposure occurs during critical developmental windows. This has profound implications, as prenatal BPA exposure has been linked to epigenetic modifications that may predispose individuals to various diseases later in life, including breast cancer [21].

Current regulatory standards for BPA exposure, such as the U.S. FDA's reference dose of 50 µg/kg/day, are increasingly questioned by the scientific community. A growing body of evidence demonstrates that BPA exhibits non-monotonic dose-response relationships, where low doses (often within the range of typical human exposure) can produce more significant biological effects than higher doses [22, 23]. This phenomenon, characteristic of endocrine-disrupting chemicals, reflects the exquisite sensitivity of hormonal systems to minute perturbations during critical developmental periods. Such findings challenge the traditional toxicological paradigm that assumes linear dose-response relationships and underscore the potential inadequacy of current regulatory thresholds in protecting public health [22].

This section provides a comprehensive analysis of BPA exposure and metabolism with several novel insights: First, it integrates recent findings on the limitations of BPA detoxification pathways, challenging the long-held assumption that conjugation renders BPA completely harmless. Second, it highlights the emerging understanding of BPA's bioaccumulation in adipose tissue, particularly breast tissue, creating an endogenous exposure source that persists beyond initial contact. Third, it critically examines the inadequacies of current regulatory standards in light of non-monotonic dose-response relationships and low-dose effects, providing a compelling argument for re-evaluating risk assessment paradigms. These insights collectively advance our understanding of how continuous, low-level BPA exposure may contribute to long-term health consequences, particularly in relation to breast cancer risk.

3. CARCINOGENIC POTENTIAL AND MOLECULAR MECHANISMS

Bisphenol A (BPA) exhibits well-documented carcinogenic potential, particularly in hormone-responsive tissues such as the breast. Its molecular structure closely resembles 17β-estradiol [18], enabling it to bind and activate both nuclear and membrane-associated estrogen receptors (ERα and ERβ) [24]. However, BPA's oncogenic effects extend far beyond simple estrogen mimicry, encompassing diverse mechanisms that contribute to tumor initiation, promotion, and progression [25]. These include genomic alterations through classical nuclear receptor signaling as well as rapid non-genomic pathways that converge to create a pro-carcinogenic cellular environment.

Through genomic mechanisms, BPA binds to nuclear estrogen receptors, forming complexes that interact with estrogen response elements (EREs) in target genes (Figure 2). This interaction modulates the transcription of key regulatory genes involved in cell proliferation and survival. Among the most significantly upregulated genes are Cyclin D1 (CCND1), which drives cell cycle progression by promoting the G1/S phase transition [26], and BCL-2, an anti-apoptotic protein that enhances the survival of genetically damaged cells [27]. Additionally, BPA upregulates progesterone receptors (PR), further amplifying hormonal signaling that stimulates mammary epithelial cell proliferation. These genomic effects disrupt normal tissue homeostasis, fostering conditions conducive to malignant transformation. Critically, these changes occur at BPA concentrations as low as nanomolar levels, which fall within the range of typical human exposure, raising concerns about the safety of current regulatory thresholds (Figure 2).

In parallel to genomic actions, BPA activates rapid non-genomic signaling pathways mediated by membrane-associated receptors, including the G protein-coupled estrogen receptor (GPER/GPR30) and epidermal growth factor receptor (EGFR) [28, 29]. Upon BPA binding, these receptors trigger instantaneous activation of downstream kinases such as MAPK/ERK1/2, PI3K/AKT, and JNK [30], which regulate essential cellular processes including proliferation, migration, and resistance to programmed cell death. The speed of these responses—often occurring within minutes of exposure—highlights the potency of BPA's non-genomic activity, particularly in aggressive breast cancer subtypes where growth factor signaling is frequently dysregulated [31]. These pathways not only accelerate tumor growth but also enhance metastatic potential by promoting epithelial-mesenchymal transition (EMT) and extracellular matrix degradation.

The combined activation of genomic and non-genomic mechanisms by BPA creates a synergistic oncogenic effect. While genomic signaling alters long-term gene expression patterns, non-genomic pathways provide immediate proliferative and survival advantages, collectively driving carcinogenesis. Moreover, emerging evidence suggests that BPA may preferentially activate these pathways in stem-like cancer cells, further exacerbating tumor aggressiveness and therapy resistance. The ability of BPA to exert these effects at environmentally relevant doses underscores its significance as a modifiable risk factor in breast cancer etiology and progression. Understanding these molecular mechanisms is crucial for developing targeted interventions to mitigate BPA-associated cancer risks and for informing more stringent regulatory policies on BPA exposure limits.

4. BREAST CANCER SUBTYPES AND BPA EFFECTS

Breast cancer represents a heterogeneous group of diseases classified by the presence or absence of key receptors, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The major molecular subtypes—Luminal A/B (ER+/PR+),

HER2-enriched, and triple-negative breast cancer (TNBC)—exhibit distinct clinical behaviors, treatment responses, and, importantly, varying susceptibility to endocrine disruptors like BPA [32]. Emerging evidence indicates that BPA influences all major breast cancer subtypes, though through divergent molecular mechanisms that reflect their unique biological characteristics.

4.1. Luminal A and B (ER+/PR+ Breast Cancers)

Luminal breast cancers, characterized by ER and/or PR expression, are particularly sensitive to estrogenic compounds. BPA mimics endogenous estrogen by binding to ERα, activating transcription of genes involved in cell proliferation (e.g., CCND1) and survival (e.g., BCL-2) [33]. Experimental studies demonstrate that BPA stimulates the growth of ER+ cell lines (MCF-7, T47D) at picomolar concentrations comparable to human exposure levels. Beyond promoting tumor growth, BPA interferes with endocrine therapies by reducing tamoxifen sensitivity, potentially driving treatment resistance. Additionally, BPA upregulates SOX2, a stemness-associated transcription factor linked to tumor initiation and poor prognosis [34]. These findings position BPA as both a tumor promoter and a contributor to therapy failure in hormone receptor-positive breast cancer.

4.2. HER2-Enriched Breast Cancers

HER2-positive tumors rely on HER2-mediated signaling for aggressive growth rather than estrogenic stimulation. Despite this, BPA exerts significant oncogenic effects in HER2+ breast cancer by modulating hypoxia-related pathways (Figure 3). Exposure to BPA induces Carbonic Anhydrase IX (CA9), an enzyme that acidifies the tumor microenvironment, thereby facilitating invasion and metastasis [35]. Furthermore, BPA activates HER3 and EGFR, amplifying HER2 signaling and potentially conferring resistance to trastuzumab, a cornerstone HER2-targeted therapy [36]. These observations underscore BPA's ability to influence growth factor pathways, demonstrating its relevance even in hormone-independent breast cancer subtypes.

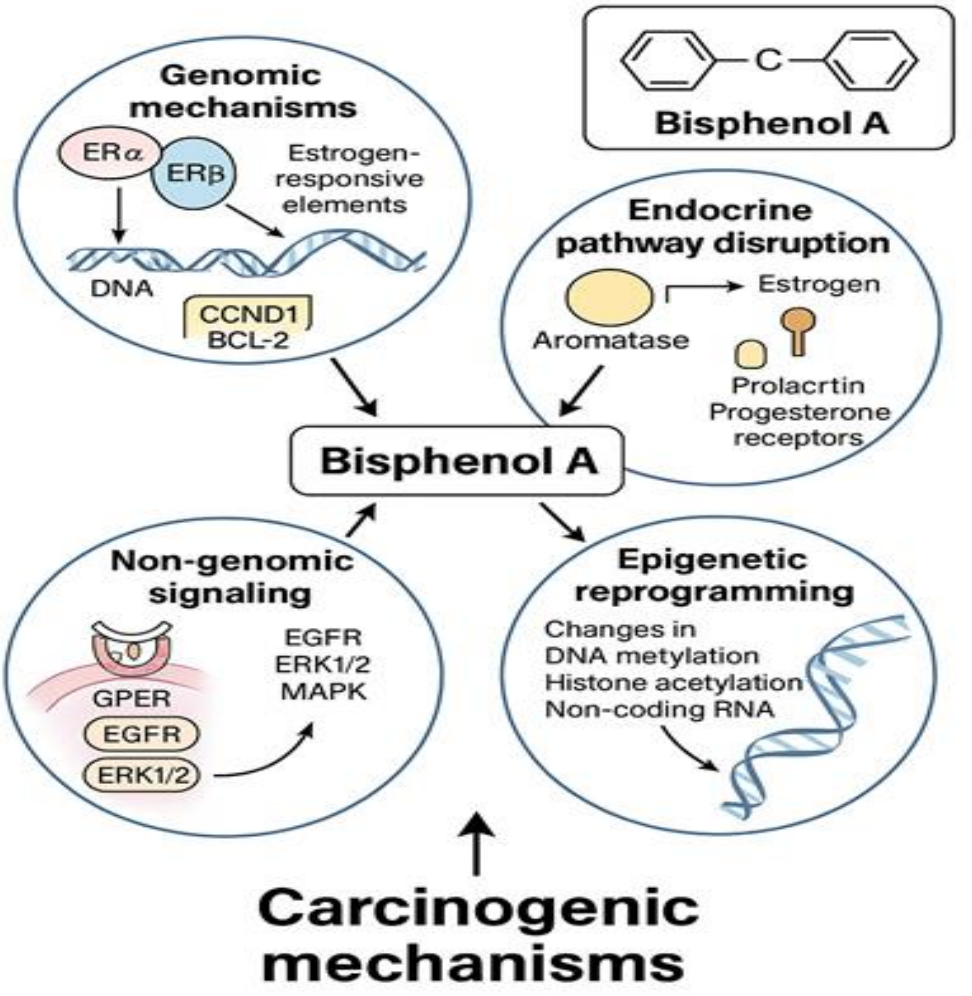

Fig. 2. The chemical structure of BPA and its primary mechanisms of action, illustrating its structural similarity to estradiol and key molecular targets involved in its endocrine-disrupting effects. The figure highlights how BPA's phenolic rings enable receptor binding and its metabolic transformation pathways that influence biological activity.

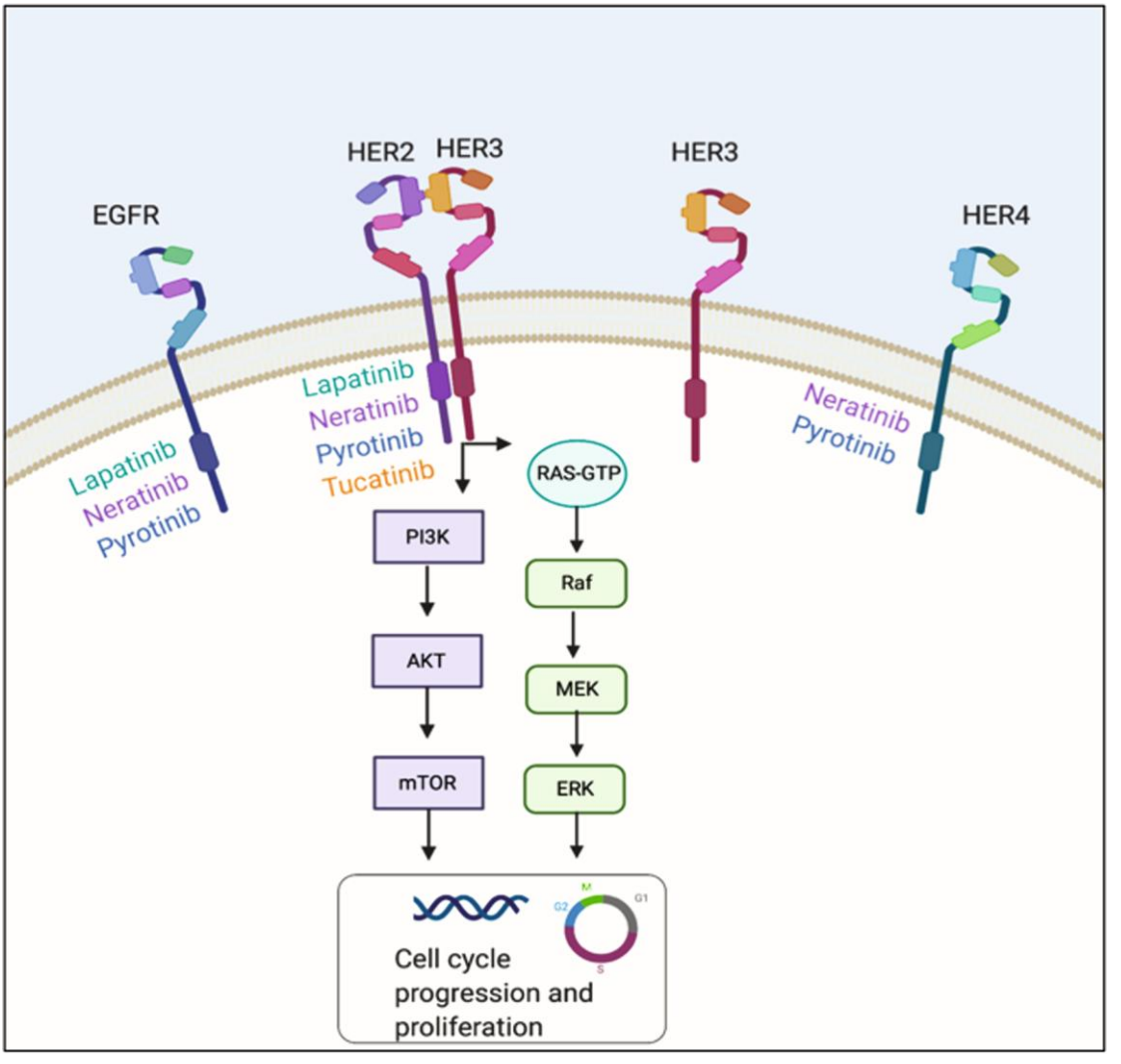

Fig. 3. Mechanism of action of HER2 tyrosine kinase inhibitors. Reprinted with permission from ref. [35], Schlam, I. and Swain, S.M., **2021.** HER2-positive breast cancer and tyrosine kinase inhibitors: the time is now. *NPJ Breast Cancer*, *7*(1), p.56. Copyright © Springer Nature.

4.3. Triple-Negative Breast Cancer (TNBC)

TNBC, which lacks ER, PR, and HER2 expression, is the most aggressive and therapeutically challenging subtype. Surprisingly, BPA remains biologically active in TNBC through estrogen-independent mechanisms, primarily via the membrane-bound G protein-coupled estrogen receptor (GPER). BPA binding to GPER triggers rapid activation of MAPK/ERK and PI3K/AKT pathways, enhancing proliferation, survival, and migratory capacity [37]. Additionally, BPA upregulates extracellular matrix-degrading enzymes (SPARC, MMP-2, MMP-9), fostering a metastatic phenotype [38]. The discovery of GPER as a key mediator of BPA's effects in TNBC highlights its potential as both a biomarker and therapeutic target in this hard-to-treat cancer [39].

The influence of BPA extends across all breast cancer subtypes, operating through receptor-specific mechanisms that converge on pro-tumorigenic signaling. In ER+ cancers, it drives proliferation and therapy resistance via classical estrogenic pathways. In HER2+ tumors, it exacerbates growth factor signaling and microenvironmental adaptation. Even in TNBC, where hormonal pathways are absent, BPA promotes malignancy through GPER-mediated signaling. This pan-subtype activity underscores BPA's role as a pervasive oncogenic agent and emphasizes the need for targeted strategies to mitigate its impact on breast cancer progression and treatment outcomes. Table 1 exhibits BPA-induced molecular pathways and effects in triple-negative breast cancer (TNBC).

5. TUMOR MICROENVIRONMENT: THE ROLE OF CANCER-ASSOCIATED FIBROBLASTS (CAFS) IN BPA-INDUCED CARCINOGENESIS

The progression and development of breast cancer are not

solely dictated by genetic mutations within cancer cells but are profoundly influenced by dynamic interactions between tumor cells and their surrounding stromal environment, collectively referred to as the tumor microenvironment (TME). Among the most critical stromal components are cancer-associated fibroblasts (CAFs), which can constitute up to 80% of the cellular fraction in certain breast tumors [17]. Unlike normal fibroblasts, CAFs undergo activation and reprogramming in response to signals secreted by cancer cells, transforming them into key orchestrators of tumor growth, invasion, and therapy resistance [40, 41]. Once activated, CAFs secrete a diverse array of growth factors, cytokines, chemokines, and extracellular matrix (ECM)-remodeling enzymes, collectively fostering a permissive niche for cancer progression. Emerging research has revealed that Bisphenol A (BPA), a pervasive endocrine-disrupting chemical, not only directly affects cancer cells but also manipulates the TME by reprogramming CAFs, thereby amplifying its carcinogenic potential [22].

5.1. BPA's Influence on CAFs

The ability of BPA to modify CAF behavior represents a critical mechanism by which it promotes breast carcinogenesis. Seminal work by Pupo et al. demonstrated that BPA exposure induces significant gene expression changes in CAFs, including the upregulation of early response genes such as c-FOS and EGR-1, as well as connective tissue growth factor (CTGF), a key mediator of fibrosis and tumor-stroma interactions [9]. Furthermore, BPA activates the GPER/EGFR/ERK1/2 signaling axis in both breast cancer cells and CAFs, stimulating proliferation and migration even in the absence of classical nuclear estrogen receptors (ERα/ERβ) [42]. These findings are particularly significant because they indicate that BPA can exert oncogenic effects indirectly by reshaping the stromal compartment, effectively "educating" non-malignant cells to support tumor growth. This stromal reprogramming suggests that BPA's carcinogenicity extends beyond direct genotoxic effects, implicating it as a potent modifier of the TME.

5.2. Paracrine Loops and the CAF-Cancer Cell Crosstalk

A hallmark of CAF-mediated tumor progression is their ability to engage in reciprocal communication with cancer cells through paracrine signaling. Activated CAFs secrete matrix metalloproteinases (MMPs), including MMP-2 and MMP-9, which degrade the basement membrane and ECM, facilitating tumor cell invasion and metastasis [43]. Additionally, CAFs produce vascular endothelial growth factor (VEGF), promoting angiogenesis and ensuring an adequate nutrient supply for the growing tumor. BPA exposure exacerbates these pro-tumorigenic functions by enhancing CAF secretion of fibronectin, collagen-modifying enzymes, and transforming growth factor-beta (TGF-β), a master regulator of epithelial-mesenchymal transition (EMT) [44]. EMT is a critical process through which cancer cells lose their epithelial characteristics, acquire mesenchymal traits, and gain invasive capabilities. By reinforcing this paracrine crosstalk, BPA fosters a self-perpetuating cycle wherein CAFs enhance cancer cell aggressiveness, and cancer cells, in turn, further activate CAFs. This bidirectional interaction not only accelerates local tumor progression but also primes distant metastatic niches, underscoring the systemic impact of BPA on breast cancer biology.

5.3. Immune Modulation and BPA-CAF Interactions

Beyond their role in ECM remodeling and angiogenesis, CAFs are increasingly recognized as key modulators of the tumor immune microenvironment. Under the influence of BPA, CAFs adopt an immunosuppressive phenotype characterized by the inhibition of cytotoxic T-cell function and the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) [45].

Table 1. BPA-Induced Molecular Pathways and Effects in Triple-Negative Breast Cancer (TNBC).

Pathway / Target	Molecular Effect	Cellular Outcome	Reference
GPER	BPA binds and activates membrane-bound GPER	Triggers non-genomic signaling	[40]
MAPK/ERK1/2 Pathway	Phosphorylation of ERK1/2 via GPER activation	Promotes proliferation and survival	[9]
PI3K/AKT Pathway	Activation of PI3K and AKT signaling	Enhances cell survival and growth	[9]
Hippo-YAP Pathway	Dephosphorylation and nuclear localization of YAP	Increases migration	[10]
NF-κB Signaling	Inhibition of NF-κB pathway via GPER	Suppresses EMT and invasiveness	[11]
SPARC, MMP-2, MMP-9	Upregulated gene expression	Enhances ECM degradation and metastasis	[43]
c-FOS, EGR-1, CTGF	BPA induces transcription via ERK/GPER axis	Stimulates proliferation	[40]
Estrogen-Related Receptor γ (ERRγ)	BPA increases ERRγ expression	Enhances MMP activity and invasion	[43]

These immune-suppressive mechanisms create an immunologically "cold" tumor environment, enabling cancer cells to evade immune surveillance and resist immunotherapeutic interventions [46]. Given the growing importance of immunotherapy in breast cancer treatment, BPA-induced CAF-mediated immune suppression poses a significant clinical challenge, potentially diminishing the efficacy of checkpoint inhibitors and other immune-based therapies.

The most insidious aspect of BPA's action lies in its ability to exert oncogenic effects even at minimal concentrations by remodeling the TME. Unlike traditional carcinogens that require direct contact with tumor cells to exert their effects, BPA can promote malignancy indirectly by altering stromal cell behavior. This means that trace levels of BPA, previously considered biologically insignificant, may still contribute to breast cancer progression by priming the stroma for tumorigenesis [7]. Moreover, chronic exposure to BPA during pre-malignant stages could establish a pro-tumorigenic stromal environment, increasing susceptibility to malignant transformation over time. These observations challenge current risk assessment paradigms, which often overlook the contribution of microenvironmental modulation in chemical carcinogenesis.

The carcinogenic potential of BPA extends far beyond its direct effects on cancer cells. By reprogramming CAFs, BPA reshapes the TME into a permissive niche that fosters tumor growth, invasion, immune evasion, and therapy resistance. This dual capacity to influence both epithelial and stromal compartments underscores the need for a more comprehensive evaluation of BPA's health risks, particularly in the context of breast cancer prevention and treatment. Future research should explore therapeutic strategies targeting BPA-induced stromal activation, as disrupting these microenvironmental interactions may offer new avenues for mitigating BPA-associated breast cancer progression.

6. NUTRITIONAL MODULATION OF BPA EFFECTS

The relationship between Bisphenol A (BPA) and human health extends beyond direct exposure to include dietary factors that either amplify or mitigate its biological effects. While much attention has focused on BPA's presence in plastics and environmental contamination [47], diet plays a dual role in this equation—serving as both a primary exposure route and a potential modulator of BPA's toxicity [48]. This complex interplay between nutrition and endocrine disruption has gained increasing scientific interest, as dietary interventions may offer practical strategies to reduce the carcinogenic impact of unavoidable environmental exposures. Understanding how specific nutrients influence BPA metabolism, bioavailability, and cellular effects is crucial for developing preventive approaches against BPA-associated breast cancer. This schematic illustrates in Figure 4 shows the dual role of diet in BPA exposure and detoxification. The left panel depicts major dietary sources of BPA contamination (canned foods, plastic-wrapped items, bottled beverages), while the right panel highlights protective food components (phytoestrogens, polyphenols, cruciferous vegetables) that compete with BPA absorption, enhance detoxification through phase II enzyme induction, or mitigate oxidative and inflammatory damage. Central pathways demonstrate BPA's metabolic fate, including intestinal absorption, hepatic conjugation, and adipose tissue storage, with protective nutrients acting at each biological interface to reduce BPA bioavailability and biological activity (Figure 4).

6.1. Diet as a Source of BPA Exposure

Food represents the most significant source of BPA exposure for the general population. Numerous studies have identified canned foods as a major contributor, since most metal cans are lined with epoxy resins containing BPA that leaches into the contents, particularly with acidic or fatty foods [37]. The degree of leaching escalates when containers are heated, such as during microwaving, or when they undergo physical wear from repeated use. Plastic-wrapped foods and beverages stored in polycarbonate bottles also release measurable amounts of BPA, especially when exposed to high temperatures during storage or transportation [38]. Pre-packaged infant formulas and baby foods are of particular concern, as early-life exposure to BPA can have lasting developmental consequences. Additionally, the lipophilic nature of BPA means that high-fat foods can facilitate its absorption, increasing bioavailability when consumed from BPA-contaminated packaging [49]. These findings highlight the need for heightened public awareness regarding food storage and preparation methods that may inadvertently increase BPA intake.

6.2. Nutrients and Foods That Exacerbate BPA's Effects

Certain dietary patterns and components can potentiate BPA's adverse effects. High-fat diets not only promote greater intestinal absorption of BPA but also contribute to obesity, a condition associated with increased adipose tissue storage of lipophilic toxins like BPA [49]. This creates a vicious cycle, as BPA accumulation in fat tissue may further disrupt metabolic homeostasis. Alcohol consumption presents another concern by impairing hepatic function and reducing the liver's capacity to detoxify BPA through glucuronidation and sulfation pathways [50]. Consequently, individuals with regular alcohol intake may maintain higher circulating levels of bioactive, unconjugated BPA. Diets deficient in antioxidants similarly exacerbate BPA toxicity by failing to counteract the oxidative stress and DNA damage induced by BPA exposure [51]. The combination of high BPA intake with a pro-inflammatory Western diet—rich in processed foods, saturated fats, and refined sugars—has been linked to amplified endocrine disruption and increased susceptibility to hormone-driven cancers like breast cancer.

These observations underscore the importance of considering dietary habits when assessing individual susceptibility to BPA's carcinogenic effects.

6.3. Protective Dietary Components

In contrast, numerous naturally occurring food compounds demonstrate protective effects against BPA-induced carcinogenesis (Table 2). Phytoestrogens, such as genistein from soy foods, compete with BPA for binding to estrogen receptors, thereby blunting its estrogenic activity [52]. This competitive inhibition has been shown to reduce BPA-stimulated proliferation in breast cancer cells. Polyphenols and flavonoids—including quercetin (found in apples and onions), resveratrol (from grapes and red wine), and epigallocatechin gallate (EGCG) in green tea—exert antioxidant effects that neutralize BPA-generated reactive oxygen species while modulating key signaling pathways like MAPK and PI3K/AKT that are dysregulated by BPA [53,54]. Cruciferous vegetables contain sulforaphane and indole-3-carbinol, which enhance BPA detoxification by upregulating phase II enzymes like glutathione-S-transferases. Dietary fiber promotes the fecal excretion of conjugated BPA metabolites and supports a healthy gut microbiome, which may further contribute to detoxification processes. Curcumin, the active compound in turmeric, exhibits both anti-inflammatory and anti-estrogenic properties that counteract multiple aspects of BPA's carcinogenic potential [55].

The mechanisms through which these protective nutrients act are multifaceted. Some compounds directly interfere with BPA's molecular interactions, while others enhance its metabolic clearance or repair resulting cellular damage. Importantly, many of these bioactive food components target the same pathways that BPA dysregulates—such as estrogen receptor signaling, oxidative stress responses, and inflammatory cascades—making them particularly effective countermeasures. This suggests that strategic dietary modifications could serve as a feasible approach to mitigate BPA-associated cancer risk, especially for individuals with unavoidable environmental exposure.

The bidirectional relationship between diet and BPA toxicity has significant implications for both risk assessment and prevention strategies. Current safety evaluations of BPA exposure rarely account for how individual dietary patterns may influence its biological impact, potentially underestimating risks for certain populations. Conversely, the identification of protective dietary factors opens avenues for nutritional interventions that could reduce susceptibility to BPA's harmful effects.

Future research should focus on quantifying the dose-response relationships of these protective nutrients and investigating potential synergies between different food components. Clinical studies are needed to evaluate whether targeted dietary interventions can measurably reduce BPA-associated health risks in human populations. Additionally, regulatory policies should consider both sides of this equation—not only limiting BPA exposure from food packaging but also promoting dietary patterns that enhance resilience against unavoidable environmental contaminants.

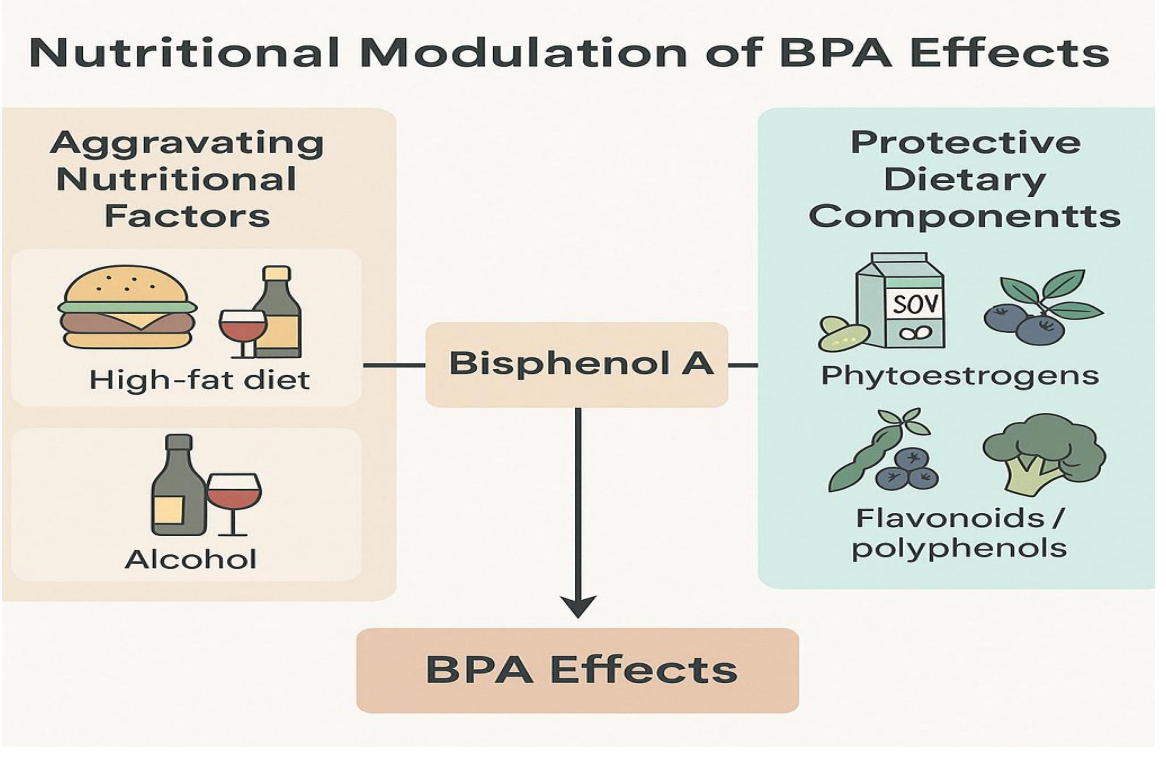

Fig. 4. Dietary Modulation of BPA Activity.

Table 2. Protective Dietary Components against BPA-Induced Carcinogenesis.

Component	Source	Action	Effect
Genistein	Soy foods	Competes with BPA at estrogen receptors	Inhibits BPA-induced cell proliferation
Quercetin	Onions, apples	Antioxidant	Reduces oxidative stress
Resveratrol	Grapes, red wine	Modulates cell signaling	Protects against BPA-induced damage
EGCG	Green tea	Antioxidant	Mitigates BPA-induced stress
Sulforaphane	Broccoli, kale	Induces detoxification enzymes	Enhances BPA clearance
Indole-3-Carbinol	Cruciferous vegetables	Modulates estrogen metabolism	Supports detoxification
Curcumin	Turmeric	Anti-inflammatory	Counters BPA's effects

Nutrition represents a critical modifier of BPA's carcinogenic potential, with specific dietary components capable of either exacerbating or mitigating its effects. A diet rich in plant-derived antioxidants, fiber, and detoxification-supporting compounds may provide a practical means of defense against BPA's endocrine-disrupting and carcinogenic activities. As research in this area progresses, dietary guidance should be incorporated into broader public health strategies aimed at reducing the cancer risks associated with ubiquitous environmental pollutants like BPA.

7. FUTURE DIRECTIONS

The growing body of evidence linking Bisphenol A (BPA) to breast cancer underscores the urgent need for further research, policy reform, and public health interventions. Future investigations should prioritize several key areas to deepen our understanding of BPA's carcinogenic mechanisms, refine risk assessment, and develop effective mitigation strategies.

First, longitudinal epidemiological studies are essential to establish definitive causal relationships between BPA exposure and breast cancer risk in humans. While animal and in vitro studies provide strong mechanistic evidence, large-scale cohort studies tracking BPA levels over time—particularly during critical developmental windows such as prenatal, neonatal, and pubertal stages—could clarify dose-response relationships and identify high-risk populations. Biomarker-based assessments, including serial measurements of urinary or serum BPA and its metabolites, should be integrated with clinical outcomes to account for cumulative exposure and metabolic variability.

Second, the mechanisms underlying BPA's non-monotonic dose response require further elucidation. Current regulatory thresholds assume linear dose-response curves, yet BPA often exerts more pronounced effects at low doses than at high ones, particularly in endocrine-sensitive tissues. Research should focus on the molecular basis of this phenomenon, including receptor saturation thresholds, epigenetic reprogramming, and crosstalk between signaling pathways. Advanced in vitro models, such as organoids and 3D tumor microenvironments, could help replicate physiological exposure scenarios and uncover thresholds for biological disruption.

Third, the role of BPA in therapy resistance demands greater attention. Emerging data suggest that BPA exposure may reduce the efficacy of hormonal therapies (e.g., tamoxifen) and targeted agents (e.g., trastuzumab) by activating alternative survival pathways. Preclinical studies should evaluate whether BPA alters drug metabolism, promotes cancer stem cell expansion, or induces adaptive mutations. Clinically, monitoring BPA levels in breast cancer patients could reveal correlations with treatment response, relapse rates, and survival outcomes, informing personalized therapeutic strategies.

Fourth, the impact of BPA analogs (e.g., BPS, BPF) and mixture effects must be rigorously assessed. Many "BPA-free" products contain structurally similar substitutes with undetermined endocrine-disrupting potential. Comparative toxicological studies are needed to evaluate whether these analogs exhibit similar or even greater carcinogenicity than BPA. Additionally, real-world exposure rarely involves isolated chemicals; interactions between BPA and other environmental pollutants (e.g., phthalates, pesticides) may have synergistic effects on breast cancer risk.

Fifth, dietary and pharmacological interventions to counteract BPA's effects should be explored in clinical settings. While preclinical studies highlight protective compounds (e.g., sulforaphane, resveratrol), their efficacy in humans remains unproven. Randomized controlled trials could assess whether specific dietary patterns (e.g., Mediterranean, high-fiber) or nutraceuticals reduce BPA bioavailability, enhance detoxification, or mitigate molecular damage in high-risk groups.

Finally, regulatory and public health policies must evolve to reflect contemporary scientific evidence. Current safety standards, often based on outdated assumptions, fail to protect vulnerable subgroups or account for chronic low-dose exposure. Advocacy for stricter manufacturing regulations,

improved biomonitoring programs, and consumer education campaigns is critical to reducing population-wide exposure. Policymakers should collaborate with researchers to establish precautionary guidelines, incentivize safer alternatives, and enforce labeling transparency for BPA-containing products. Addressing the multifaceted challenges posed by BPA requires a concerted effort spanning basic science, clinical research, and public policy. By prioritizing these future directions, the scientific and medical communities can advance preventive strategies, improve patient outcomes, and ultimately reduce the global burden of BPA-associated breast cancer.

8. CONCLUSION

The extensive body of research on Bisphenol A (BPA) underscores its significant role as an endocrine disruptor with profound implications for breast cancer development and progression. This review highlights BPA's multifaceted mechanisms, including its ability to mimic estrogen, alter gene expression, and disrupt cellular signaling pathways, even at exposure levels deemed "safe" by regulatory agencies. Importantly, BPA's carcinogenic effects extend across all breast cancer subtypes—ER+, HER2+, and TNBC—through both hormonal and non-hormonal pathways, emphasizing its broad oncogenic potential. A critical emerging aspect is BPA's influence on the tumor microenvironment, particularly its ability to activate cancer-associated fibroblasts (CAFs) and promote immune evasion. By reshaping stromal interactions, BPA creates a permissive niche for tumor growth, invasion, and therapy resistance. These findings challenge the traditional view of BPA as solely an estrogen-mimicking agent, revealing its broader role as a tumor microenvironment modulator. Nutritional factors further complicate the BPA-cancer relationship. Diets high in fat or alcohol may exacerbate BPA's effects, whereas bioactive compounds like genistein, sulforaphane, and curcumin show promise in mitigating its harm. This duality underscores the importance of dietary interventions as a practical strategy to reduce BPA-associated risks. Despite growing evidence, regulatory frameworks remain outdated, failing to account for low-dose chronic exposure, non-monotonic dose responses, and vulnerable populations (e.g., fetuses, children). There is an urgent need for stricter regulations, alternatives to BPA-based plastics, and public health initiatives to minimize exposure. Future research should prioritize longitudinal human studies, mechanistic investigations into BPA's role in therapy resistance, and clinical trials evaluating dietary and pharmacological countermeasures. BPA represents a modifiable environmental risk factor for breast cancer. Addressing this threat requires a multidisciplinary approach, integrating scientific research, policy reform, and public education to safeguard current and future generations from preventable harm.

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

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