Carcinogenic effects of bisphenol A in breast and ovarian cancers (Review)

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Abstract. Endocrine-disrupting chemicals (EDCs) are exogenous chemical compounds ubiquitously found in everyday life of the modern world. EDCs enter the human body where they act similarly to endogenous hormones, altering the functions of the endocrine system and causing adverse effects on human health. Bisphenol A (BPA), the principal representative of this class, is a carbon-based synthetic plastic, and a key element in manufacturing cans, reusable water bottles and medical equipment. BPA mimics the actions of estrogen on multiple levels by activating estrogen receptors α and β. BPA regulates various processes, such as cell proliferation, migration and apoptosis, leading to neoplastic changes. Considering genetic mechanisms, BPA exerts its functions via multiple oncogenic signaling pathways, including the STAT3, PI3K/AKT and MAPK pathways. Furthermore, BPA is associated with various modifications of the reproductive system in both males and females. These alterations include benign lesions, such as endometrial hyperplasia, the development of ovarian cysts, an increase in the ductal density of mammary gland cells and other preneoplastic lesions. These benign lesions may continue to develop to breast or ovarian cancer; the effects of BPA depend on various molecular and epigenetic mechanisms that dictate whether the endocrine or reproductive system is impacted, wherein preexisting benign lesions can become cancerous. The present review supports the need for continuous research on BPA, considering its widespread use and most available data suggesting a carcinogenic effect of BPA on the female reproductive system. Although most studies on BPA have been conducted *in vitro* with human cells or *in vivo* with animal models, it can be argued that more studies should be conducted *in vivo* with humans to further promote understanding of the impact of BPA.

Contents

1. Introduction

The use of plastic dates back to the 16th century, when men were shaping natural rubber with their hands and polymerizing it into objects of utility (1). Baekeland produced the first synthetic polymer in 1907 in Belgium (1). Plastics are polymers, which are chains of molecules with each chain composed of carbon, silicon, oxygen and/or hydrogen; and the process of linking chains together is termed polymerization. Combining plastic polymers with plasticizers, antioxidants, fillers, colorings or flame retardants, creates a variety of plastic materials with multiple properties. The risks for human health can be derived from the monomeric building block [such as bisphenol A (BPA)], the additives (such as plasticizers) or a combination of the two (such as antimicrobial polycarbonate) (1,2).

Endocrine-disrupting chemicals (EDCs) represent ubiquitous natural or human-made plastic reagents that are absorbed

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by the human body and interfere with hormonal actions, resulting in disruptive effects at multiple levels of the endocrine system (3). Changes in the levels of the naturally present hormones circulating in the human body may be implicated in the rising incidence of numerous cancers of the reproductive system in both males and females (4). Disturbances in estrogen functions are associated with the occurrence of multiple preneoplastic or neoplastic lesions in females, such as breast, ovarian, endometrial or cervical cancer, which are considered to be highly responsive to changes in hormone levels (4).

BPA, or 4,40-dihydroxy-2,2-diphenylpropane, is an organic synthetic plastic monomer that was first synthesized in the 1890s as a synthetic estrogen. However, the effects of this compound on the reproductive system of rats were only first reported in the 1930s (5); and later studies demonstrated on mice the induction of oxidative stress, DNA damage and epigenetic changes in oocytes (6). The 1940s industry was using BPA to make polymers, such as epoxy resins or polycarbonate, as a flame retardant, an antioxidant, or an inhibitor of polyvinyl chloride polymerization (7). In current practice, BPA is successfully used in manufacturing various consumer products, such as baby bottles, reusable plastic bottles, internal can coatings, dental materials and different medical devices (7). In Italy, in 2002, 0.25-1.2 mg/kg BPA, derived from plastic pipes, was found in drinking water (8). Various studies have suggested that it is likely >90% of human exposure to BPA is due to food contamination, and the remaining exposure is due to dust ingestion, dermal absorption or dental surgeries (8,9).

Considering the increasing prevalence of various health problems associated with exposure to BPA, with the majority leading to cancer or other significant issues, there is an imperative need for the present review. The latest studies in this field were searched to determine if current evidence is conclusive or if more extensive studies are required to demonstrate the impact of BPA on individuals and society as a significant public health problem.

2. BPA: Everyday exposure

BPA is an omnipresent chemical compound in everyday life of the modern world. Humans can be exposed to this chemical compound via various routes, such as oral, transdermal or inhalation. Food packaging, dental materials, thermal paper, toys, healthcare equipment, bottles for infants or children, and even dust represent significant sources of BPA contamination (8,10). The most notable source of exposure to BPA is food (9), of which canned food and drinks represent considerable sources (9,11,12). In addition, BPA is present in fresh food, such as eggs, milk, vegetables and fruits, due to the watering of soil with polluted water (11); and there are considerable traces of BPA in cardboard boxes that store food (12). The food industry relies heavily on BPA in manufacturing food cans; it is a key element in food preservation as it is used to coat the inside of cans, thus preventing direct contact of the food with metal, and it also determines the structural strength of the can and thermal stability (13). Dust from laminated floors, electronic equipment, epoxy resins and adhesives, and paint can also contain BPA (14). Exposure of infants or children to dust from various materials used for building or to everyday items they interact with, such as baby bottles, plastic drinking bottles, eyeglass wear, toys or bicycle helmets, have been demonstrated to be higher compared with other age categories (15,16). It has been demonstrated by previous studies that BPA blood levels in children are higher compared with adults (17,18).

The dental industry also represents a significant source of BPA exposure via dental fillings or other key materials used in the manufacturing of dental crowns (19); bisphenol A-glycidyl methacrylate (bis-GMA) is a primary compound used in this industry that may break down or be contaminated with BPA. Vast amounts of bis-GMA have been found in the saliva of patients following a dental visit (20).

3. Key roles of BPA in the pathogenesis of multiple disorders

To the best of our knowledge, only a limited number of studies on humans have investigated the association between BPA exposure during either intrauterine life or the postnatal period and its effects on general health. BPA has been associated with multiple metabolic disorders, such as polycystic ovarian syndrome, recurrent miscarriages and endometrial hyperplasia, as well as obesity and general health disorders, such as an altered immune system, cardiovascular disease, infertility, hormone-dependent tumors, diabetes in adults and precocious puberty (21-23). Women with polycystic ovarian syndrome (PCOS) present with higher circulating testosterone levels compared with healthy women. This particular group of female patients also exhibit higher circulting levels of serum BPA compared with women without PCOS, and it is understood that elevated levels of androgens decrease the clearance of BPA (24). Furthermore, women with endometriosis exhibit higher levels of serum BPA, suggesting an association between this chemical compound and the disease (25). A previous study indicated that patients with high urine levels of BPA have a higher chance of implantation failure during *in vitro* fertilization treatments (22). Nevertheless, exposure to BPA at an early age may be associated with multiple metabolic disorders. Associations of BPA exposure with adiposity, an increased body-fat percentage, a high body mass index and abdominal circumference, and numerous neurological implications, such as anxious or depressive behavior, has been observed in this category of young patients with the age ranging from 8 to 14 years (23,26).

Extensive research over the last decade has demonstrated a close association between BPA exposure and the incidence of different neoplasias, particularly breast and ovarian cancers, and also likely prostate cancer, although this has not been completely concluded (27,28). Either natural or anabolic steroids are acknowledged to be involved in the occurrence of these neoplasias (27-30).

4. BPA: A key element in female cancers

BPA in ovarian cancer and other benign ovarian lesions. It has been demonstrated that exposure to 25-250 ng/kg BPA per day in the prenatal period in rats can induce changes in the gross ovarian anatomy (31). It is well documented that exposure to BPA in the prenatal period is associated with cystic endometrial hyperplasia, ovarian cysts, and a reduction in the primordial pool of follicles in mouse ovaries, indicating an association between BPA and increased proliferation of

ovarian cells mediated by the estrogenic pathway (31,32). Studies have shown an increase in the percentage of ovarian tissue that is occupied by antral follicles and also a decreased percentage of corpora lutea in rats groups treated with BPA for 3 months compared with controls, which is suggestive of a reduced number of oocytes (31,32). Prenatal exposure to BPA can also result in a notable increase of unilateral or bilateral ovarian bursae filled with blood, which is a sign of reproductive ageing in 6-month-old mice (33). Furthermore, other studies have suggested that following accidental exposure to BPA, there is an increase in meiotic disturbances in mice, such as aneuploidy in oocytes (34,35).

Ovarian cancer was reported in 2018 to be the seventh leading cause of cancer-associated mortality worldwide, and its 5-year survival rate is <20% in women (36). Several studies have suggested an association between exposure to BPA and ovarian malignancy, as BPA mimics the effects of estrogen (37,38). In addition, human ovarian cancer cells express elevated levels of estrogen receptors (ERs) compared with normal or benign ovarian lesion cells (36). Long-term exposure to BPA could lead to an increased incidence of cystic endometrial hyperplasia or ovarian cysts, which are premalignant lesions (39,40). In both normal and malignant ovarian cells, there are two isoforms of ERs, ERα and ERβ, and ERβ expression in both normal and benign lesion cells is higher compared with ERα (41-43). The expression of ERα is higher in malignant tumors cells (44). ERα acts as an oncogene, while ERβ acts like a tumor suppressor. In normal cells, the expression of ERβ is significantly higher compared with ERα, but in ovarian tumoral cells the expression of ERα is 40-60% higher than ERβ (44). ERα expression is higher in malignant cells compared with normal cells, while ERβ expression is higher in normal cells compared with malignant cells (44). Multiple studies have shown that ERβ is considered to offer a protective role against cancer by promoting inhibition of cell migration and proliferation, or by inducing apoptosis (36,45). Increased levels of both ER isoforms can be found in ovarian cancer compared with normal non-neoplastic ovaries, and the expression of this receptor is associated with unfavorable progression (46). Studies have reported that estrogens are capable of activating the proliferation of surface epithelial cells of ovaries and also mediating growth response and gene expression to produce changes in cancer cells (47,48). In addition, it is understood that in postmenopausal women, estrogens can induce an increasing incidence of ovarian cancer (49,50). Furthermore, multiple studies on animal models suggest that continuous exposure to BPA from the early stages of life can lead to a higher prevalence of alterations in the estrous cycle. Thus, BPA induces changes in ovarian morphology and ovulation, but also an increased incidence of endometriosis, cystic endometrial hyperplasia, proliferation lesions of the oviduct, stromal polyps, atypical hyperplasia, leiomyomas or adenomyosis (39,51).

Analysis via PCR has shown that mRNA is altered at different levels during the processes of ovarian tumorigenesis. Upregulated mRNAs, such as CDK4, cyclin D1, cyclin A, proliferating cell nuclear antigen, E2F transcription factor (E2F)3 and E2F1, are associated with the cell cycle and cell proliferation, while other downregulated mRNAs, such as p21, GADD45 and Weel-1, are also associated with cell proliferation; and all of these cell cycle genetically-programed mechanisms have been shown to be modified by exposure to BPA (52). Multiple studies have demonstrated that BPA plays an important role in ovarian cancer by inducing activation of cell signaling pathways, such as the MAPK/ERK and PI3K/AKT pathways (53). Prenatal exposure to BPA can lead to inhibition of the expression of apoptotic genes, such as CAD, FAS, RAIDD, FADD, BOK and caspase, and can induce the expression of pro-survival genes, such as Mcl-1 and Bcl-x1, and also the growth of ovarian cancer cells via the specific signaling axis ER-CXCL12-CXCR-4 (54,55).

Ovarian cancer is considered to be highly fatal as it is often diagnosed in terminal stages when intraperitoneal metastasis is present (56). Intraperitoneal metastasis is induced by a decrease of E-cadherin, which leads to a loss of cell adhesion (57). The switch from E-cadherin to N-cadherin expression is a key element in the dynamics of neoplastic cells (57). N-cadherin can induce the overexpression of matrix metalloproteinases (MMPs), which alters the extracellular matrix and the basal membrane, therefore promoting tumor invasion (57). MMP-9 and MMP-2 differ from other types of MMPs due to their ability to degrade type IV collagen (58,59). It has been demonstrated that BPA stimulates granulosa lutein cells so that they express MMP-9, and elevated levels of MMP-9 and MMP-2 are associated with the metaplastic transformation of normal ovarian cells (39,60-62).

Not only BPA is associated with the occurrence of ovarian cancer; other EDCs, such as methoxychlor [1,1,1-trichlor-2,2-bis-(4-methoxyphenyl)ethane; MXC] and triclosan (TCS) act synergistically. These chemical compounds are ubiquitous in everyday products, such as toothpaste, deodorants and hygiene products (23). Recent studies have shown these two compounds at relatively low doses can induce the growth of BG-1 ovarian cancer cells by regulating p21, cyclin D1 and Bax genes, which are associated with the cell cycle and apoptosis (62,63). In experimental models, BG-1 cells treated with TCS or MXC resulted in cyclin D1 upregulation, p21 downregulation and activation of Bax gene transcription. In addition, the ER antagonist ICI 182,780 can reverse the MXC and TSC-induced alterations of these particular genes, which suggests that the actions of these compounds are mediated by signaling pathways that are ER-dependent (63).

BPA in breast cancer. Although endogenous estrogen has a higher potency compared with xenoestrogen, the latter is ubiquitous in nature and is more dangerous due to its resistance to enzymatic or chemical degradation (64).

Breast cancer is considered to be the most prevalent cancer type in female patients, and the main risk factors are due to genetic, lifestyle or environmental influences (65). EDCs are considered to contribute to the increasing incidence of breast cancer, particularly in critical periods of breast development, when mammary gland cells are the most predisposed to atypical differentiation (66-68). *In vitro* studies have demonstrated that exposure of human mammary gland cancer cells to BPA increases proliferation and oxidative stress, even at low doses (demonstrated for 10^{-10} M) for long-period exposure, of minimum 60 days (69,70).

In immunohistochemical analysis of animal model, mammary gland tumors are investigated for the presence

or the absence of three key receptors. In experimets with animal models, the long term effect of BPA was observed in gestational monkeys, demonstrating a significant increase in the density of mammary buds, and also an overall increase in the volume of mammary epithelium in newborns (71). A study on rats revealed that exposure during intrauterine life to different doses of BPA (2.5, 25, 250 and 1,000 μg/kg/day) can lead to an exponential increase in the number of hyperplastic ducts at postnatal day 50 in a dose-independent manner and also a significant increase in these numbers even at a low dose at postnatal day 90 (72). Another study on rats demonstrated that the incidence of mammary tumors would increase following the administration of different doses of BPA (0.25, 2.5, 25 and 250 μg/kg/day) during both the gestational and lactation periods. Preneoplastic lesions were already observed at day 50. Atypical ductal hyperplasia or neoplastic modifications, like ductal carcinomas *in situ*, in mammary gland cells were diagnosed in the rats exposed to BPA. At postnatal day 200, malignant tumors were observed in female rats exposed to a low BPA dose of only 0.25 μg/kg/day, which were histopathologically diagnosed as benign fibroadenoma or adenocarcinomas. These findings demonstrate a direct association between BPA and breast cancer (73).

ERα and ERβ are expressed in greater than 60% of human breast cancers and are ligand-regulated transcription factors that control breast cancer proliferation (74,75). Multiple studies have suggested that progesterone and estradiol are key factors in the malignant transformation of mammary gland cells, by increasing division and proliferation of cells in both mature and immature human breast tissue (74,75). It has been demonstrated that the therapy of estrogen replacement in postmenopausal women leads to an increased proliferation of terminal duct lobular units that represent the target site of breast cancer (74,75). Additionally, breast cell proliferation increases in adulthood, when levels of progesterone and estradiol are higher. Estradiol determines the proliferation of mammary cells, which are positive for ERα expression. This effect is determined indirectly by growth factors, which are produced as a response to estrogenic regulation or directly by promoting the transcription of genes involved in the cell cycle, such as c-Myc (76). Furthermore, ERs are known to determine non-genomic signaling events in the extra-nuclear site of mammary cancer cells, which stimulate anti-apoptotic and proliferative signaling pathways as a response to growth factors or ligand binding. This non-genomic action is associated with the rapid response by activating estradiol pathways, which involves the action of MAPK, Src, PI3K, protein kinase-C and heterotrimeric G-proteins in the membrane or cytoplasm of target cells (77). Some biological effects, including cell growth, DNA synthesis, cell death and cell cycle progression, and also processes that are associated with ER cytoplasm re-localization, are attributed to activation by estradiol stimulation (78).

BPA functions as an xenoestrogen, and a number of studies with animal models have shown that it has important implications in breast cancer (79,80). Results from animals studies have been used to predict what may occur in the human body, which lead to finding that the greater risk of breast cancer is associated with mutations of the susceptibility genes BRCA1 and BRCA2 in mammary gland cancer cells. These two genes are considered to act as tumor suppressor genes, resulting in hereditary ovarian or breast cancer syndrome (HBOC) if they undergo mutations in the germline, which is inherited in an autosomal-dominant manner. Individuals that present HBOC syndrome also have a higher risk of developing prostate cancer (8.6% for BRCA1 mutations and 20% for BRCA2 mutations), pancreatic cancer (1-3% for BRCA1 mutations and 2-7% for BRCA2 mutations) and melanoma (81). The incidence of HBOC syndrome accounts for approximately 6% of all breast cancer cases; however, the incidence of breast cancer accounts for greater than 70% of all HBOC cancer cases (79-83). Previous studies have demonstrated that women that exhibit mutations in BRCA1 and BRCA2 have a higher susceptibility to the negative effects of exposure to environmental BPA (79,80,82). Furthermore, other studies have reported that the effects of BPA on adult breast tissue, both normal or cancerous, are associated with cell proliferation, the induction of chemoresistance in ER-positive cells and also the increase of mammosphere size (82,83).

BPA acts through activating vascular endothelial growth factor, which is associated with angiogenesis in breast tumor, activation of the MAPK signaling pathway, STAT3 signaling, DNA repair, and changes in genes associated with apoptosis by DNA methylation (84-87). The expression of the long non-coding RNA HOX transcript antisense RNA, a key player in different neoplasias, including breast and ovarian cancer, inactivation of p53, and cell death or modulation of proliferation kinetics in human breast epithelial cells are also stimulated by BPA (84-87). These studies on the effects of BPA in humans suggest that BPA can play an important role in breast epithelial cells and carcinogenesis.

Considering the carcinogenic effect of different plastics on the human body, BPA is not the only EDC with important effects on health. Studies suggest other polychlorinated biphenyls, such as PCB-153 at a relatively high concentration (35 μM), are associated with cell proliferation by regulating ERK1/2 activation (86-88). Furthermore, multiple studies suggest that organochlorine insecticides, such as p,p'-DDT (dichloro-diphenyl-tri-chloroethane) (DDT), p,p'-DDE and chlordane, are risk factors for breast cancer (87,88). It has been suggested that DDT can lead to cancer progression by interfering with androgen signaling pathways and promoting the proliferation of breast cancer cells (88). Notably, it has been reported that in patients with breast cancer, exposure to DDT has negative effects on overall survival (88). Most available data in the literature suggest that organochlorine compounds influence the progression and pathogenesis of breast cancer.

5. Conclusions

EDCs are natural or synthetic chemical compounds that interact with the human endocrine system and are associated with various hormone-related diseases (89). BPA is the most widespread chemical compound among all EDCs, and substantial evidence indicates that BPA plays a negative role in various female reproductive system disorders and should be the subject of extensive research (90). BPA carries out effects via multiple mechanisms, most of which involve BPA binding to ERs and interfering with nuclear receptors (91), leading

to an alteration in metabolism, the action of hormones or by inducing epigenetic dysregulation (92). Xenoestrogens mimic the effects of estrogen in humans, hence the name (93). BPA, the most widespread EDC in the modern world, can induce benign modifications in human ovaries, such as the progressive proliferation of the oviducts, endometriosis, cystic endometrial hyperplasia or ovarian cysts (94). Furthermore, evidence has suggested that BPA is implicated in the occurrence of ovarian cancer (95).

Moreover, *in vivo* studies with human cells and *in vivo* studies with animal models have demonstrated a direct association between exposure to environmental doses of BPA and a high incidence of breast cancer (96). In summary, research on the carcinogenic effects of BPA is a subject of lengthy debate, deciding on dose and the time-line between exposure and neoplasia, although most available data suggest it is associated with an increased risk of cancer incidence (97). Considering that most studies are conducted either *in vitro* on human cells or *in vivo* on animal models, it would be necessary to determine the effects of BPA through *in vivo* analyses, on humans domestic or job-related exposed for a definitive and improved understanding of its mechanisms of action. For example, determining serum BPA levels in individuals highly exposed would be important. Afterwards, in case of increased concentrations, measuring the mRNA expression of uridine diphosphate-glucuronosyl transferase, a resultant enzyme reaction product of BPA glucuronidation in the liver, would be necessary (98).

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MCD, RCP and AP substantially contributed to the conception of the work, designed the review, and revised and edited the final manuscript. CMa, FS, RIP and CMe researched the literature and drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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