



ONCOLOGY | REVIEW ARTICLE

Breast cancer and environmental contamination: A real connection?

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Abstract: Breast cancer is the most prevalent cancer among women and the second cause of cancer-related death in the world. This review describes the effects of bisphenol A, phthalates, and parabens, important environmental chemicals that have been associated with developing breast cancer. With more or less success, most of the studies have failed to establish a definitive correlation between cause and effect. The reason for these discrepancies and lack of consistency seems clear in some cases but is blurred in others. Here, we outline the facts reported in the literature and suggest that more studies should be done to clarify gene-environment interactions that could lead to breast cancer, and to identify groups of women that could be at higher risk according to their epigenome, since it seems that environmental chemicals are more harmful than previously thought.

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PUBLIC INTEREST STATEMENT

Breast cancer is the most prevalent cancer among women and the second cause of cancer-related death in the world. Unfortunately, different environmental pollutants have been associated with developing breast cancer. Among those environmental toxins are a group of chemical consumer products that can be found in household items, personal care products, pharmaceuticals, insecticides, food and beverage cans and bottles, and drinking water. Several of them behave like estrogens, hormones that are required for the development of female secondary sexual characters that have also been linked to breast cancer. It has been suggested that they can increase the risk of breast cancer during periods of major susceptibility of the breast and even pass to infants through breast milk. Nowadays, the association between environmental toxic chemicals and breast cancer is still controversial and is imperative to determine if this association is real.

Subjects: Bioscience; Environmental Studies and Management; Health and Social Care; Medicine

Keywords: breast cancer; endocrine disrupting compound; environmental toxins

1. Introduction

Breast cancer is the most frequent type of cancer among women in the world and its incidence has increased in the past 25 years. The highest incidence is in non-Hispanic white and non-Hispanic black women, followed by American Indian/Alaska Native, Hispanic/Latina, and Asian/Pacific Islander. These incidence differences in breast cancer between race and ethnic categories are more probably related with lifestyle factors (Gray, Rasanayagam, Engel, & Rizzo, 2017; American Cancer Society, 2017–2018). In addition, environment, epigenetic modifications, miRNAs, and single nucleotide polymorphisms are associated with increased risk in developing breast cancer. Other mayor risk factors for breast cancer are age, dense breasts, longer time breast tissue exposure to estrogen (menarche before age 12; menopause after age 55), giving birth late in life or never given birth, no breastfeeding, hormone replacement therapy, breast/chest radiation therapy, obesity, sedentary lifestyle, stress, and shiftwork (Fletcher & Dudbridge, 2014; Gray et al., 2017; Loi et al., 2005; Montenegro et al., 2016; O'Brien et al., 2016; Samantarrai, Dash, Chhetri, & Mallick, 2013). In addition, only 5–10% of breast cancers are hereditary, and most of them are due to mutations in BRCA1 and BRCA2 genes, but other genes are also associated (Economopoulou, Dimitriadis, & Psyrris, 2015).

Since estrogens have been linked to breast cancer, it is important to consider that several synthetic chemicals behave like estrogens, increasing the risk of breast cancer during periods of major susceptibility of the breast, such as puberty and *in utero*. Additionally, some of those chemicals can pass to infants through breast milk (Fourth National Report on Human Exposure to Environmental Chemicals, 2017; Rudel, Gray, et al., 2011; Rudolph, Chang-Claude, & Schmidt, 2016). Thousands of different toxic environmental synthetic chemicals are used daily, and as the use of them has risen, so have been the rates of breast cancer. Hence, the research on the association among these new substances and breast cancer incidence is crucial. Importantly, nonindustrialized countries present lower rates of breast cancer compared to industrialized countries (Gray et al., 2017; Rodgers, Udesky, Rudel, & Green, 2018; Rudel, Ackerman, Attfield, & Brody, 2014; Witorsch & Thomas, 2010). However, it is difficult to determine how the exposure to toxic environmental chemicals affects the risk in developing breast cancer. The environment is a complex world and we are daily exposed to different toxic chemicals, and by the time breast cancer is diagnosed, a long period has passed, complicating the possible correlations.

The purpose of this report is to review the literature on some of the most common and still used environmental consumer product chemical toxins, bisphenol A (BPA), phthalates, and parabens, that have been associated with the development of breast cancer (Table 1). An overview of research articles about these three compounds and their findings are summarized in Tables 2–4, respectively. Nowadays, the association between environmental toxic chemicals and breast cancer is still controversial and is imperative to determine if a particular chemical, or a combination of them, is causing breast cancer.

Table 1. Sources of exposure of bisphenol A, phthalates, and parabens

| Chemical compound | Source of exposure |
|--------------------------|---|
| Bisphenol A | Dentistry composites, paints, plastics, toys, food and beverage cans, polycarbonate beverage bottles, and drinking water |
| Phthalates | Household items, detergents, medical devices, pharmaceuticals, insecticides, toys, personal care products, food processing or packaging, and drinking water |
| Parabens | Personal care products, foods, beverages, and pharmaceuticals |

Table 2. Bisphenol A and breast cancer research findings

| Chemical compound | Experimental material | Exposure | Research finding | Authors |
|-------------------|---|--|--|--------------------------|
| BPA | Nonmalignant contralateral breast tissue of patients with primary breast cancer lesion | <i>In vitro</i> | BPA exposure induced gene expression patterns associated with apoptosis evasion, microenvironmental stress, and deregulation of the cell cycle. These alterations were associated with large breast tumors, suggesting an important role of BPA in the aggressiveness of the tumor | Dairkee et al. (2008) |
| | MDEC cells (progenitor human breast epithelial cells differentiated into breast epithelial cells), and 48 breast cancer cells | <i>In vitro</i> | Heritable effects of BPA on nuclear localization of ERα and differential gene expression of potential biomarkers | Weng et al. (2010) |
| | HRBEC cells (human nonmalignant breast epithelial cells from high-risk women) | <i>In vitro</i> | Low concentrations of BPA can have undesirable health consequences | Goodson et al. (2011) |
| | HRBEC cells (human nonepithelial cells from high-risk women), and T47D breast cancer cells | <i>In vitro</i> | BPA induced abnormal expression of several proteins involved in cell survival, proliferation, and apoptosis | Dairkee et al. (2013) |
| | SKBr3 and MDA-MB-231 human breast cancer cells | <i>In vitro</i> | BPA promoted <i>in vitro</i> migration and mesenchymal transition of breast cancer cells | Zhan et al. (2015) |
| | Sprague Dawley rats | Gestation days 10–21 (female offspring received 7,12-dimethylbenz(a)anthracene at postnatal day 50 or 100) | Prenatal exposure to BPA increased mammary cancer susceptibility and alterations in the expression of proteins implicated in cell proliferation | Betancourt et al. (2010) |
| | Sprague Dawley rats, and MCF-7 human breast cancer cells | 90-day-old rats | BPA induced HOTAIR expression in MCF-7 cells and in mammary glands | Bhan et al. (2014) |
| | Sprague Dawley rats | Pregnant dams, newborn pups until adulthood | Toxicological effects were observed at the highest BPA doses. Sample contamination affected the interpretation of the effect of lower concentrations of BPA | Churwell et al. (2014) |
| | Sprague Dawley rats | Gestation day 6 to postnatal day 90 | Only high doses of BPA were able to depress gestational and postnatal body weight gain and affect ovary and serum hormones | Delclos et al. (2014) |
| | Albino rats | Female adults for 8 weeks | BPA induced structural and proliferation alterations of mammary glands | Ibrahim et al. (2016) |
| | Wistar rats | Perinatal exposure | BPA exposure increased mammary growth in rodents, suggesting an increased risk for developing breast cancer in women | Mandrup et al. (2016) |
| | CD1 mice and MCF-7 breast cancer cells | Gestational days 9–26 | <i>In utero</i> exposure to BPA induced modifications in the epigenome of the mammary gland. BPA also induced epimutations in MCF-7 cells | Doherty et al. (2010) |
| | FVB/N mice, and MCF-7 human breast cancer cells | Fetal mice (offspring were treated with 7,12-dimethylbenz(a)anthracene and MCF-7 cells were subcutaneously injected) | BPA exposure augmented the risk of developing mammary cancer in mice | Weber and Keri (2011) |
| | C57BL/6 mice and the B6 (CAST7) or C7 strains | Two weeks prior to mating and during pregnancy until embryonic days 9.5 and 12.5 | Fetal exposure to BPA induced epigenetic changes in the embryo and placenta | Susiarjo et al. (2013) |
| BALB/c mice | Postnatal day 3 | BPA induced an increase in tumor weight due to alterations in the immune system | Palacios-Arreola et al. (2017) | |

BPA: Bisphenol A.

Table 3. Phthalates and breast cancer research findings

| Chemical compound | Experimental material | Exposure | Research finding | Authors | |
|-------------------|---|---|--|---|-----------------------|
| Phthalates | MCF7 human breast cancer cells and MCF10A human normal cells | <i>In vitro</i> | BBP induced the expression of human ER α , probably through changes in the methylation pattern of the promoter region | Kang and Lee (2005) | |
| | MCF-7 human breast cancer cells | <i>In vitro</i> | MEHP activated human PPAR α and PPAR γ . Its toxicological consequences in the breast are complex | Venkata et al. (2006) | |
| | MCF-7, T-47D, ZR-75-1, MDAMB-231, MDA-MB-435, and SK-BR-3 breast cancer cells | <i>In vitro</i> | BBP and dibutyl phthalate induced proliferation, migration, invasion, and tumor formation. Stimulation of the AHR downstream-signaling pathway, an oncogenic mechanism independent from their estrogenic activities | Hsieh, Tsai, Hsu, Kuo, Lee, et al. (2012) | |
| | R2d human breast epithelial cancer stem cells, MCF-7 human breast cancer cells, and HUVECs human umbilical vein endothelial cells | <i>In vitro</i> | BBP exposure altered the expression of certain genes involved in proliferation, epithelial-mesenchymal transition, and angiogenesis signaling by more than 10-folds in R2d cells. Induced the viability, invasion and migration, and tube formation <i>in vitro</i> , and angiogenesis <i>in vivo</i> of R2d and MCF-7 cells | Hsieh, Tsai, Hsu, Kuo, Hsi, et al. (2012) | |
| | MCF-7 and MDA-MB-231 human breast cancer cells | <i>In vitro</i> | <i>In vitro</i> DEHP exposure induced proliferation of MCF-7 and MDA-MB-231 cells. DEHP also suppressed tamoxifen induced apoptosis in both cell types | Das et al. (2014) | |
| | MDA-MB-231 human breast cancer cells, HUVECs human umbilical vein endothelial cells, and 4T1 mouse mammary tumor cell line | <i>In vitro</i> | BBP was able to remodel the breast cancer tumor microenvironment, influencing the efficacy of chemotherapy | Hsu et al. (2015) | |
| | MCF-7 and MDA-MB-231 human breast cancer cells, and Nu/Nu immunodeficient mice | <i>In vitro</i> | Phthalates stimulated breast tumor-initiating cells in human breast cancer cell cultures and xenograft tumors | Wang et al. (2016) | |
| | Sprague Dawley rats | Gestational day 14 to postnatal day 3 | DEHP, BBP, and DNP affected sexual differentiation | Gray et al. (2000) | |
| | Wistar rats | Gestational day 6 to lactation day 21 | DEHP exposure only increased the number of ovarian atretic tertiary follicles; no other effects were observed | Grande et al. (2006) | |
| | Wistar-Imamichi rats | Postnatal days 22-41 and to 84 | Inhalation of DEHP may alter the onset of puberty and postpubertal reproductive functions | Ma et al. (2006) | |
| | C57/B16 mice | Gestational days 17-19 | MEHP exposure induced early ovarian senescence and mammary hyperplasia | Moyer and Hixon (2012) | |
| | Clinical studies | Puerto Rican girls with premature breast development (case-control study) | | Probable association between plasticizers with estrogenic and antiandrogenic activities and premature breast development in girls | Colón et al. (2000) |
| | | Girls in early puberty (case-control study) | | MMP in girls may cause early puberty in Taiwanese girls | Chou et al. (2009) |
| | | Mexican women with breast cancer (case-control study) | | Exposure to diethyl phthalate may be associated with higher risk of breast cancer | López-Carrillo (2010) |
| | | Women from the AN Medical Center (case-control study) | | Exposure to the parent compound of the phthalate metabolite MEHP could be associated with breast cancer | Holmes et al. (2014) |
| | Girls with central precocious puberty and prepubertal (multicenter cross-sectional study) | | Phthalates exposure was not associated with premature puberty in girls | Lomenick et al. (2010) | |
| | Mexican-American newborns (longitudinal birth cohort study) | <i>In utero</i> | Prenatal phthalate exposure induced differential DNA methylation patterns in newborns | Solomon et al. (2017) | |

AHR: Aryl hydrocarbon receptor; BBP: butyl benzyl phthalate; DEHP: di-(2-ethylhexyl) phthalate; DNP: di-isononylphthalate; MEHP: mono-(2-ethylhexyl) phthalate; MMP: monomethyl phthalate; ER: estrogen receptor; PPAR: peroxisome proliferator-activated receptor.

Table 4. Parabens and breast cancer research findings

| Chemical compound | Experimental material | Exposure | Research finding | Authors |
|-------------------|---|---|---|--------------------------------|
| Parabens | HRBEC cells (human nonmalignant breast epithelial cells from high-risk women) | <i>In vitro</i> | Low concentrations of methylparaben can have undesirable health consequences | Goodson et al. (2011) |
| | MCF-7 human breast cancer cells | <i>In vitro</i> | Even though parabens possess estrogenic properties, global gene expression patterns are not equal to 17 β -estradiol | Pugazhendhi et al., 2007 |
| | MCF-7 human breast cancer cells | <i>In vitro</i> | Five parabens were present in human breast tissue at concentrations capable to stimulate MCF-7 cells proliferation | Charles and Darbre (2013) |
| | MCF-7, T-47-D, and ZR-75-1 human breast cancer cells | <i>In vitro</i> | <i>In vitro</i> long-term exposure of parabens can influence proliferation, migration, and invasive properties of human breast cancer cells | Khanna et al. (2014) |
| | MCF-7 human breast cancer cells and MCF-10A nonmalignant cells | <i>In vitro</i> | Differences in the expression of cell cycle and apoptotic genes were induced with parabens and 17 β -estradiol in MCF-7 cells, but not in MCF-10A cells | Wróbel and Greoraszczyk (2014) |
| | BT-474 human breast cancer cells | <i>In vitro</i> | HER ligands enhanced the potency of butylparaben to induce oncogene expression and breast cancer cell proliferation, suggesting that parabens might be toxicologically active at low levels | Pan et al. (2016) |
| | Sprague Dawley rats | Perinatal, prepubertal, and pubertal periods, and from birth to lactation | Low-dose exposure to methyl paraben induced alterations in mammary histology and transcriptome | Gopalakrishnan et al. (2017) |
| | Clinical studies | Women from general population | Elevated levels of native parabens were associated with the use of skin lotions, suggesting that their regular use preserve elevated concentrations regardless of parabens short half-lives | Sandager et al. (2011) |
| | | Breast cancer tissue of women from England | Different parabens were quantifiable, with the highest levels for <i>n</i> -propylparaben and methylparaben. The source of the paraben cannot be identified | Barr et al. (2012) |

2. BPA

BPA is found in dentistry composites, paints, plastics, and toys and is used to cover food and beverage cans, polycarbonate beverage bottles, and no long ago, baby bottles, and infant formula packaging. BPA has also been detected in air, house dust, rivers, and drinking water (Matsumoto, Adachi, & Suzuki, 2005; Rodriguez-Mozaz, de Alda, & Barceló, 2005) (Table 1). Considering its broad use in food-related storage items, the exposure of humans to BPA is ubiquitous and has been detected in urine (Doerge, Twaddle, Vanlandingham, & Fisher, 2010; Hengstler et al., 2011; Lakind & Naiman, 2011; Rudel, Gray, et al., 2011; Rudel, Fenton, Ackerman, Euling, Makris, 2011; Vandenberg et al., 2010).

BPA is considered an estrogen-disruptor compound (EDC), since it binds to estrogen receptors (ERs), but its affinity is 1,000–10,000 lower than endogenous estrogen (Hengstler et al., 2011; Melzer et al., 2011). Following oral administration in live animals and humans, BPA is rapidly and almost completely metabolized in the gastrointestinal tract to an inactive form, and its primary metabolite does not bind to ER receptors, neither *in vivo* nor *in vitro* (Doerge et al., 2010; Frederick et al., 2014; Hengstler et al., 2011; Yang & Fisher, 2014). In humans, BPA derivatives are extensively excreted in urine, and after 3 days without eating packaged foods, BPA's urine levels decrease about 65%. Other studies have demonstrated that BPA is mostly eliminated at higher concentrations through sweat (Frederick et al., 2014; Genuis, Beesoon, Birkholz, & Lobo, 2012; Rudel, Fenton, et al., 2011; Stahlhut, Welshons, & Swan, 2009; Yang & Fisher, 2014). BPA has also been detected in premature infants, breast milk, amniotic fluid, placental tissue, and umbilical cord (Calafat et al., 2009; Ikezuki, Tsutsumi, Takai, Kamei, & Taketani, 2002; Schönfelder et al., 2002; Sun et al., 2004). Another way of BPA exposure is through inhalation and skin absorption, routes of more concern, since unconjugated BPA may circulate longer periods in bloodstream compared to ingested BPA (Hengstler et al., 2011; Vom Saal & Welshons, 2014).

A study performed by Churchwell et al. (2014) showed that the presence of BPA in food does not exert any pathological effects in the fetus, even though the doses of BPA orally exposed to the rat expecting dam and newborn pups were much higher than an expected human daily intake. Furthermore, studies performed by the FDA's National Center for Toxicological Research researchers have shown that the BPA derived from food that could pass to the fetus is extremely low. Even the feeding of pregnant rodents with 100–1,000 times more BPA than what a woman could be exposed do not lead to detectable active BPA in the fetus after mother's exposure; in addition, it is considered that human infant exposure is as much as 92% less than earlier estimations (Churchwell et al., 2014; Delclos et al., 2014; Melnick et al., 2002).

On the other side, several studies suggest that BPA increase the risk of breast cancer, especially if the exposure is early in life. There are animal studies indicating that fetal environmental exposure, and also during lactation, can affect mammary gland development, even at low doses, and those changes were associated with development of breast cancer during adulthood (Acevedo, Davis, Schaeberle, Sonnenschein, & Soto, 2013; Betancourt, Eltoun, Desmond, Russo, & Lamartiniere, 2010; Mandrup, Boberg, Isling, Christiansen, & Hass, 2016; Paulose, Speroni, Sonnenschein, & Soto, 2015; Weber & Keri, 2011). In addition, rats exposed to BPA in womb presented abnormalities in adult mammary tissue and alterations in the milk protein content by the time they were feedings their pups (Kass, Altamirano, Bosquiazzo, Luque, & Muñoz-de-Toro, 2012). It has also been shown that mice prenatal exposure to BPA alters gene transcription of epithelial cellular genes and genes that are associated with the stroma of the mouse fetal mammary gland. Considering that BPA is an EDC, after birth, BPA exposure alters the sensitivity to estradiol-dependent mammary gland development and progesterone-dependent mammary cell proliferation. Additionally, BPA affects both ER-dependent and ER-independent pathways (Ibrahim, Elbakry, & Bayomy, 2016; Paulose et al., 2015; Zhang et al. 2015).

In the study by Jenkins, Wang, Eltoun, Desmond, and Lamartiniere (2011), adult mice chronically exposed to low doses of BPA showed accelerated mammary tumorigenesis and

metastasis, and only higher doses increased apoptosis. It has also been shown that the expression of several different genes involved in hormone-mediated pathways, cell proliferation, apoptosis, and cancer were altered in normal or cancerous human breast cells that were exposed to low levels of BPA. And the cells coming from the noncancerous breast also presented a gene expression profile similar to the pattern found in the development of aggressive tumors (Dairkee, Luciani-Torres, Moore, & Goodson III, 2013; Dairkee et al., 2008; Weng et al., 2010). In addition, Palacios-Arreola, Nava-Castro, Del Río-Araiza, Pérez-Sánchez, and Morales-Montor (2017) induced the growth of a mammary adenocarcinoma tumor implanted in the mammary gland of mice and demonstrated that a single dose of BPA at postnatal day 3 affected the immune system and led to an increased tumor size during adulthood. The BPA exposure did not alter puberty onset but affected the expression of ER α in immune cells. These results suggest that early life BPA exposure can induce breast cancer development by altering the antitumoral immune response.

It has also been shown that BPA exposure alters the imprinting of particular human and rodent genes, such as LAMP3, important protein in invasive cancers (Dhimolea et al., 2014; Susiarjo, Sasson, Mesaros, & Bartolomei, 2013; Weng et al., 2010). In addition, studies performed in human MCF-7 breast cancer cell line, and in mice mammary glands exposed to BPA *in utero*, showed alterations in the expression of the histone methyltransferase EZH2 (Doherty, Bromer, Zhou, Aldad, & Taylor, 2010) and the transcription of the long noncoding RNA HOTAIR (Bhan et al., 2014), both linked to breast cancer. Thus, it is possible that BPA has other important targets affecting breast tumorigenesis.

3. Phthalates

Phthalates are a group of chemicals used to make polyvinyl chloride flexible and stable. They are found in different household items, medical devices, dentistry, vinyl flooring, automobiles, detergents, adhesives, insecticides, and toys. Phthalates are also used in personal care products, because they increment spreadability. Foods can be contaminated with phthalates by processing or packaging, and when food is heated in plastic containers in the microwave, they can be released into aqueous solution (Table 1). Milk, medications and nutritional supplements, and ground and drinking water can contain phthalates. These chemicals can also be absorbed through the skin or breathed in from house dust or fumes (Breast Cancer & the Environment Research Centers, 2007; Center for Disease Control and Prevention, 2015).

Among the most common phthalates are butyl benzyl phthalate (BBP), di-*n*-butylphthalate (DBP), di-(2-ethylhexyl)phthalate (DEHP), diethylphthalate (DEP), di-isobutylphthalate (DiBP), di-isodecylphthalate, di-isononylphthalate, di-methylphthalate, di-*n*-hexylphthalate, and di-*n*-octylphthalate. The different phthalates are metabolized undergoing some specific biotransformations and are eliminated in urine and feces (Breast Cancer & the Environment Research Centers, 2007; Janjua, Frederiksen, Skakkebaek, Wulf, & Andersson, 2008; Meeker, Calafat, & Hauser, 2012); they have also been detected in human amniotic fluid and human breast milk (Hines, Calafat, Silva, Mendola, & Fenton, 2009; Silva et al., 2004). It has been demonstrated by Cirillo, Fasano, Castaldi, Montuori, and Amodio (2011) that packed school meals contained DEHP and DBP with percentage values higher than the allowed tolerable daily intake.

BBP and DBP behave as weak estrogens in cell culture systems; DBP, DiBP, and BBP also bind weakly to androgen receptors (AR). Moreover, several phthalates simultaneously behave as agonists and/or antagonists of one or more hormone receptors, and others do not bind to either ER or AR (Czernych, Chraniuk, Zagożdżon, & Wolska, 2017; Okubo, Suzuki, Yokoyama, Kano, & Kano, 2003; Takeuchi et al., 2005). By binding to AR *in utero* and during lactation, phthalates alter rodent male sexual development, affecting the reproductive tract and fertility (Gray et al., 2000). The study by Gray, Laskey, and Ostby (2006), in female rats, showed that oral administration of DBP during long periods, at doses that induce sexual alterations in male rat, triggers abortion in more than 50% female rats. Moyer and Hixon (2012) showed that pregnant mice orally exposed to

mono-(2-ethylhexyl) phthalate (MEHP), during gestational days 17–19, resulted in sexual alterations in F1 adult females, leading to a reduction in fertility and mammary gland hyperplasia. Other studies have shown that exposure to DEHP *in utero*, and prepubescent rats, retards the onset of puberty (Grande, Andrade, & Talsness, 2006; Ma, Kondo, & Ban, 2006), and BBP exposure *in utero* affects rat mammary gland morphology, retards puberty, and alters gene expression profile to a more carcinogenic type (Moral et al., 2011). Studies in humans have shown that girls going through thelarche at earlier years had elevated levels of phthalates compared to girls without premature breast development (Chou, Huang, Lee, Wu, & Lin, 2009; Colón, Caro, Bourdony, & Rosario, 2000). But a report by Lomenick et al. (2010) suggested that phthalate exposure was not associated with girls premature puberty.

BBP also binds to aryl hydrocarbon receptor (AhR) and induces cancer stem-cell proliferation enhancing metastasis (Wang et al., 2016). A study by Hsieh, Tsai, Hsu, Kuo, and Lee, et al. (2012), performed with MDA-MB-231 ER(–) breast cancer cell line, demonstrated that BBP and DBP treatments stimulated AhR, activating the downstream cAMP-PKA-CREB1 signaling pathway, inducing cell proliferation, migration, invasion, and tumor formation by non-estrogenic mechanisms. Additionally, it has been shown that phthalates activate PPAR- α (peroxisome proliferator-activated receptor) and can exert carcinogenic effects by other cellular pathways that do not involve ER and AR (Das, Singh, & Thakur, 2014; Venkata et al., 2006).

In order to clarify the effects of BBP, the most widely used phthalate, on genes transcriptions in human breast cancer cells, Hsieh, Tsai, Hsu, Kuo, Hsi, et al. (2012) analyzed gene expression changes induced by BBP treatment to a whole human genome cDNA microarray. They focused in genes that changed their transcription pattern in more than 10-fold compared to the control and found upregulation and downregulation of particular genes associated with cell proliferation, epithelial–mesenchymal transition, and angiogenesis. It has also been shown that phthalates induce epigenetics alterations. Kang and Lee (2005) demonstrated that phthalates can induce changes in the epigenome of normal (MCF10A) and breast cancer cells (MCF-7) after BBP exposure, leading to demethylation of ER α promoter. In addition, human studies on cord blood samples from newborns showed that *in utero* phthalate exposure modifies the DNA methylation pattern of BRCA1 gene and others genes involved in cancer, endocrine function, inflammatory response, and male fertility (Solomon et al., 2017).

The hospital-based case-control study by López-Carrillo et al. (2010) evaluated the presence and concentration of phthalate metabolites in women’s urine samples and suggested an association between DEP and an increased risk in developing breast cancer. Additionally, the hospital-based case-control study by Holmes et al. (2014) suggested an association between DEHP exposure (parent phthalate of MEHP metabolite) and breast cancer, even though the study was limited due to the small sample size.

Since it is known that estrogens induce drug resistance to the chemotherapeutic drug tamoxifen (Shiau et al., 1998), the action of phthalates was investigated in MCF-7 ER(+) breast cancer cells. It was demonstrated that BBP, DBP, and DEHP induce cell proliferation in MCF-7 cells, but not in ER(–) MDA-MB-231 breast cancer cells, and phthalates were also able to inhibit tamoxifen induced apoptosis in MCF-7 cells, demonstrating that phthalates mimicked estrogen effects. In addition, it has been demonstrated that BBP induced chemoresistance by decreasing doxorubicin/cyclophosphamide-induced apoptosis by altering the breast cancer microenvironment in mice (Hsu et al., 2015).

4. Parabens

The five most commonly used parabens are methylparaben, ethylparaben, *n*-propylparaben, *n*-butylparaben, and isobutylparaben. Parabens are found in personal care products, foods, beverages, and pharmaceuticals (Table 1). They act as preservatives due to their bactericidal and fungicidal properties (Błądzka, Gromadzińska, & Wąsowicz, 2014; Shen, Jiang, Mao, Pan, & Cao, 2007).

Parabens have been measured in human breast milk, urine, amniotic fluid, serum, and seminal fluid. The concentrations of parabens in adult's urine tend to be higher in women than in men, and lower in children than in adults, probably due to differences in the use of personal care products. Since parabens are quickly eliminated from the body, the exposure time is reduced. But, considering that they are constantly used, we have them continually present in our bodies (Calafat, Ye, Wong, Bishop, & Needham, 2010; Philippat et al., 2013; Sandager et al., 2011; Schlumpf et al., 2010). Parabens are considered weak EDCs, since they bound 10,000–100,000 times less strongly to ERs compared to estrogen (Routledge, Parker, Odum, Ashby, & Sumpter, 1998; Watanabe et al., 2013). But, since picogram concentrations of estradiol/gram of breast tissue and microgram concentrations of parabens/gram of breast tissue have been detected, the high concentration exposure could compensate the lower potency of parabens (Barr, Metaxas, Harbach, Savoy, & Darbre, 2012; Boberg, Taxvig, Christiansen, & Hass, 2010; Harvey & Everett, 2012). The more abundant parabens present in human primary breast cancer tissues have been *n*-propylparaben and methylparaben (Darbre, 2003; Sandager et al., 2011). In addition, the axilla was the prevalent region where *n*-propylparaben was detected and correlates with the fact that the incidence of breast cancer in the outer quadrant of the breast exceeds 50% of breast cancer cases in the United Kingdom. These results are consistent with the postulate that dermal applications of personal care products in underarm are coincident with this route of exposure, since oral route will implicate metabolic processes in the gut and liver that will produce *p*-hydroxybenzoic metabolite (Darbre, 2005; Darbre & Charles, 2010). However, the study by Barr et al. (2012) also mentioned that the actual source of paraben cannot be identified, because 17.5% of the patients never used underarm cosmetics. The presence of parabens in the majority of the breast tissue samples does not mean they caused breast cancer but requires further investigation (Barr et al., 2012; Harvey & Everett, 2012).

Parabens have also been involved in cell growth and proliferation, and since combinations of them are present in human breast tissue at concentrations that can induce proliferation of MCF-7 breast cancer cell line, it implies that they could affect human breast tissue. In addition, certain parabens can induce migration and invasion of human breast cancer cells and affect apoptosis (Charles & Darbre, 2013; Darbre & Harvey, 2014; Gopalakrishnan et al., 2017; Khanna, Dash, & Darbre, 2014; Wróbel & Gregoraszczyk, 2014). The study by Goodson et al. (2011) showed that methylparaben induces cell cycling and favors apoptosis evasion in human breast epithelial cells, important phenomena for malignant transformation. In addition, DNA damage, chromosome aberrations, and gene expression profiles that resemble estrogen stimulation after exposure to methyl- and butylparabens have been reported (Pugazhendhi, Sadler, & Darbre, 2007).

Another relevant aspect to consider is that the human epidermal growth factor receptor HER2, overexpressed in ~25% breast tumors and considered a detrimental prognostic indicator, enhanced the potency of parabens by inducing oncogene expression and breast cancer cell proliferation *in vitro*, indicating that lower doses of parabens are required to induce breast cancer (Pan et al., 2016). Then, the reevaluation of xenoestrogens in the presence of HER ligands should be considered, since studies evaluating parabens alone can underestimate their proliferative effects.

5. Conclusions

Thus far, the relationship between environmental and toxic chemicals is still controversial. It constitutes a great challenge to determine if particular chemical, or a combination of them, is causing breast cancer. And since breast cancer incidence increases as countries move forward into industrialization, environmental toxic exposure constitutes a relevant public health concern.

An important aspect to be evaluated is the type of exposure that people usually faces, either at home, at work or just walking, or driving. And in view of the fact that exposures are usually a mixture of chemical compounds, with a wide range of concentrations and variable periods of exposure, the interpretation of the results gets harder. In that way, epidemiological studies should divide participants according to the type of exposure to get more reliable and convincing results. Furthermore, the direct measurement of the toxic chemical exposure during the years previous of

breast cancer diagnosis is missing. This is an important aspect to consider, since some chemicals accumulate over time, and tumorigenic phenotype acquisition usually takes years. Moreover, given the multifactorial nature of the problem, it should be relevant to determine the genome haplotype of the participants in any study, to find whether polymorphisms show predisposition or resistance to the environmental insult being tested.

Additionally, it would be important to estimate how exposure during the most critical and vulnerable periods of breast development (in womb, newborn, puberty) correlates with the risk of developing breast cancer during adulthood. In that way, protocols should be standardized evaluating the range of doses of the environmental chemicals adjusted in regard to different stages of development. Also, from the point of view of predictive chemistry, it would be important to improve the tools to identify the potential chemicals that could induce cancer, as well as methods to measure them, avoiding possible contaminations. In this context, it would be interesting to know the methylation profile of the individual's genome to evaluate whether particular changes in imprinting fingerprints correlate with cancer outcome upon chemical exposure.

In an effort to determine the breast cancer potential of environmental chemicals, the studies performed in animals are very helpful, but have to be more precise, considering the windows of vulnerability of the mammary tissue and the correlation between doses at which humans could be daily exposed. In other words, even though there are many examples of mechanistic explanations and discoveries done in mouse models that effectively mimic human diseases, significant differences remain and have to be considered when analyzing the data. These differences have all been shown to be, in various aspects, associated with cancer, such as mouse life span, differences in gut microbiota, the effect of the central nervous system on chronic inflammation and possibly cancer, and the immune system, central to the tumorigenesis and its progression, the epigenome regulatory differences, and lately, the systemic effects of tumors on the organism. However, in spite of this, it is still worth to rely on animals studies as bona fide approximations.

Some studies did not show positive epidemiological evidence. The epidemiological investigations should consist of single cohorts evaluating exposures early in life with continual assessments to be more precise and informative and considering unexposed populations to discard the baseline risk. Also, different but relevant aspects should be all together evaluated, such as alteration of mammary gland development and the activation of particular receptors, like ER and AhR, which impact different cellular pathways leading to breast cancer. Since endocrine disruption as well as genotoxicity play critical roles in cancer development, both biological activities have to be evaluated to determine how the cellular pathways are affected to find a way to counteract them. The alternative approaches should evaluate diverse and relevant biological activities transversely to multiple chemicals, such as estrogenic/antiestrogenic activity and DNA damage and epimutations. If we are able to comprehend the early events that could lead to genetic- or epimutations that could induce breast cancer, we will have more opportunities to avoid those risks and prevent the development of breast cancer later in life. Thus, in addition to previous suggestions outlined above, all available technology aimed to determine epigenetic modifications under various conditions should be attempted.

More studies should be done to search for the extensive number of toxic chemicals to understand the gene-environment interactions that could lead to breast cancer and identify groups of women that could be at higher risk. In addition, it is really important to understand how the environment impacts or affects breast cancer risk, and for that we need to count on better chemicals tests, because it seems that environmental chemicals are more harmful than previously thought.

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