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Implication of Environmental Estrogens on Breast Cancer Treatment and Progression

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Abstract

Breast cancer is the most diagnosed malignancy among women in the United States. Approximately 70% of breast tumors express estrogen receptor alpha and are deemed ER-positive. ER-positive breast tumors depend upon endogenous estrogens to promote ER-mediated cellular proliferation. Decades of research have led to a fundamental understanding of the role ER signaling in this disease and this knowledge has led to significant advancements in the clinical use of antiestrogens for breast cancer treatment. However, adjuvant breast cancer recurrence and metastatic disease progression due to endocrine therapy resistance are prominent and unresolved issues. The established role that estrogens play in breast cancer pathogenesis explains why some patients initially respond to endocrine therapy but also why a significant number of patients become refractory to antiestrogen treatment. It is been hypothesized that exposure to environmental steroid hormone mimics and/or acquired mechanisms of resistance may explain why endocrine therapy fails in a subset of breast cancer patients. This review will highlight: 1) the relationship between ER signaling and breast cancer pathogenesis, 2) the implication of environmental exposures on steroid hormone regulated processes including breast cancer, and 3) the unresolved issue of endocrine therapy resistance.

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Conflict of interest

The authors declare no conflicts of interest.

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Keywords

endocrine disruption; anti-androgens; estrogens; estrogenicity; estrogen receptor- α ; breast cancer

Introduction

Estrogen and other steroid hormones are lipophilic small molecules that are primarily produced in the gonads and adrenal glands (Miller and Auchus, 2011). Steroid hormones are well known to play prominent roles in reproduction, organ development, and the regulation of normal physiological processes. Organs and tissues such as the brain (Solum and Handa, 2002), lungs (Carey et al., 2007), gonads (Alves et al., 2013; Li et al., 2013), and breast (Macias and Hinck, 2012) are just a few examples of targets which steroid hormones act upon. Some of these same hormones have also been shown to be critically involved in the development or progression of steroid hormone-dependent diseases such as prostate (Shi et al., 2013) and breast cancer (Lippman et al., 2001). For example, cumulative lifetime exposure to estrogens has been associated with an increased risk of breast cancer in postmenopausal women (Lippman et al., 2001). The importance of estrogens in breast cancer progression is highlighted by the fact that approximately 70% of all breast tumors express the estrogen receptor and proliferate in the presence of estrogenic hormones (Dowsett et al., 2010). There has been increasing interest and debate as to whether environmental exposure to endocrine disrupting chemicals (EDCs) can alter normal steroid hormone regulated processes and contribute to estrogen-dependent diseases such as breast cancer. Here, we will discuss the relationship between estrogen and breast cancer, the potential role of environmental estrogen mimics on breast cancer progression, and review the current understanding of suspected estrogenic EDCs on altering normal human physiology and estrogen regulated pathways.

Transport and Metabolism of Estrogen

Due to the lipophilic nature of steroid hormones, they can readily diffuse across cellular membranes and into systemic circulation (Oren et al., 2004). Unlike peptide hormones, which are generally highly water-soluble, steroid hormones are poorly soluble in blood due to their lipophilic nature. Therefore, most steroid hormones are reversibly bound to carrier proteins in the plasma which are in equilibrium with the free and bound state of a given hormone (Mendel, 1989). Albumin, sex hormone-binding globulin, and corticosteroid-binding globulin are examples of carrier proteins that transport steroid hormones in the blood (Hammond, 2016). However, it is the unbound, or free steroid, that diffuse out of the capillaries to elicit their biological effects on target tissues and cells expressing their cognate receptors, including sex steroid nuclear receptors.

Some estrogen target tissues are known to modify estrogens to hydroxylated catechol estrogens via oxidation reactions by cytochrome P450 enzymes (Lepine et al., 2004). Furthermore, conjugation of estrogens and their oxidized metabolites can be achieved by sulfotransferase and UDP-glucuronosyltransferase phase II enzymes which generally inactivate and convert these hormones into polar, water soluble metabolites that aids in their

excretion (Cheng et al., 1998; Lepine et al., 2004). Estrogens that have been conjugated with a sulfate or glucuronide moiety are representative of the most common types of conjugated circulating estrogens (Lepine et al., 2004).

The Estrogen Receptor

ER β

There are two main subtypes of ER known as estrogen receptor α (ER α) and estrogen receptor β (ER β) (Pinton et al., 2018). The first reports of the cloning and sequencing of ER α occurred in 1986 by two separate groups (Green et al., 1986; Greene et al., 1986), while Kuiper *et al.* were the first to clone and identify ER β from rat prostate several years later in 1996 (Kuiper et al., 1996). Recent reports have identified at least five isoforms of ER β that further add to the complexity of the possible regulatory roles of ER β (Baek et al., 2015). However, most research groups do agree that ER β primarily exhibits antiproliferative, pro-apoptotic, and tumor suppressive functions by opposing and antagonizing ER α mediated pathways (Nakajima et al., 2011; Paech, 1997). It has been suggested that ER β achieves these opposing actions by sequestering estrogen (E2) or by forming heterodimers with ER α to exert a negative regulatory effect on ER α function (Miller et al., 2017; Omoto et al., 2003). Despite these findings, major issues with the cell lines and inadequately validated antibodies for ER β were recently described (Nelson et al., 2017). Nelson *et al.* showed that one of the main antibodies used to detect ER β , NCL-ER-BETA, is non-specific for this receptor (Nelson et al., 2017). Using antibodies verified by liquid chromatography–mass spectrometry, Nelson *et al.* also showed that ER β was not expressed in either MCF-7 or LNCaP cell lines which have been commonly used to study ER β and potentially calls into question some of the conclusions made in studies using NCL-ER-BETA antibody (Nelson et al., 2017). The findings by Nelson *et al.* likely explain much of the uncertainty and inconsistencies regarding the role of ER β in breast and prostate cancer (Haldosen et al., 2014) and contributes to the rationale for this review focusing on ER α in the context of EDCs instead.

ER α 66

ER α 66 is a nuclear receptor and transcription factor that is primarily localized to the cellular nucleus and is comprised of six unique domains that serve separate functions (Green et al., 1986; Greene et al., 1986). The A/B domain includes the region of the receptor known as activation function-1 (AF-1) that contains a serine residue at position 118 (Ser¹¹⁸). Phosphorylation of Ser¹¹⁸ (ER α -P-Ser¹¹⁸) has been shown to be critical for proper function of ER where this receptor modification is likely controlled in part by the mitogen-activated protein kinase pathway, with CDK7 or IKK- α (Chen et al., 2000; Weitsman et al., 2006). Weitsman *et al.* used chromatin immunoprecipitation to show that ER α -P-Ser¹¹⁸ binds to known ER α coactivators proteins, specifically p300 and steroid receptor coactivator-3 (Yi et al., 2015), to provide evidence of the functional involvement of ER α -P-Ser¹¹⁸ in estrogen regulated pathways (Weitsman et al., 2006). The DNA binding domain (DBD) is in the C domain of ER α 66 and is responsible for binding to the estrogen response element (ERE) located at the promotor region of estrogen regulated genes. The interaction of the DBD with an ERE occurs through recognition of the consensus palindromic sequence identified as

GGTCAnnnTGACC (O'Lone et al., 2004). Additionally, the D domain hinge region has been implicated in the recruitment of transcription factors such as c-Jun and contains the nuclear localization sequence which aids in the translocation of ER α to the nucleus (Burns et al., 2011).

The ligand binding domain (LBD) and activation function-2 (AF-2) region of ER α 66 are both located in the E domain of this receptor. However, the functions of the LBD and AF-2 of ER α 66 are primarily activated upon binding of endogenous estrogens (Delfosse et al., 2015; Kumar et al., 2011). Brzozowski *et al.* were the first to report the crystal structure for the LBD of ER α 66 in complex with E2 using x-ray diffraction (Brzozowski et al., 1997). They noted that the helical arrangement of ER α 66 formed a hydrophobic ligand binding cavity that complemented the lipophilic characteristic of E2. The shape of this binding site cavity appeared to favor the formation of specific hydrogen bonds with E2 which are key to orienting the bound hormone (Brzozowski et al., 1997; Kumar et al., 2011). The binding of a high affinity agonist such as E2 induces a conformational change in ER that stabilizes the positioning of helix 12 (H12) which has been shown to be a critical LBD helix whose positioning directly influences the transcriptional activity of ER α 66 (Delfosse et al., 2015). The stabilization of H12 exposes a hydrophobic groove between helices H3, H4, and H12 that recognizes and recruits coactivators that contain LxxLL helical motifs to the AF-2 region (Delfosse et al., 2015; Warnmark et al., 2002). In contrast, the binding of antagonists destabilizes the positioning of H12 which prevents LxxLL coactivator association with ER and favors the recruitment of transcriptional corepressors as observed with the ER antagonist tamoxifen and its more potent active metabolite, 4-hydroxytamoxifen (Shang et al., 2000). The final domain of ER α 66 is known as the F domain which has been suggested to be involved in modulating the positioning of H12 and activity of ER α 66 (Nichols et al., 1998). Targeted mutations of the F domain have been shown to alter the affinity of E2 and ER antagonists such as tamoxifen or even preventing the interaction of some coactivator proteins (Koide et al., 2007; Montano et al., 1995; Schwartz et al., 2002).

The Role of Estrogen and the ER Pathway in Breast Cancer

Breast cancer is the most commonly diagnosed malignancy among women in the United States (US) with an estimated 266,000 new diagnoses and 41,000 deaths in 2018 alone (Siegel et al., 2018). Despite these numbers, the mortality rate for breast cancer has been steadily declining over the last three decades (Siegel et al., 2018). The reported decline in the mortality rate has largely been attributed to early detection, significant advancements in patient treatment, and a greater understanding of the biological mechanisms driving different breast tumor types (DeSantis et al., 2015).

Endocrine Therapy Resistance and Recurrence in HR+ Breast Cancer

Although ER α -P-Ser118 is an example of a prognostic marker that was reported to predict which breast cancer patients might benefit from endocrine therapy at diagnosis (Yamashita et al., 2008), additional biological markers are needed to identify which patients are more likely to experience a recurrence of their cancer. For instance, Pan *et al.* showed that there is a persistent risk of recurrence and death from breast cancer for at least 20 years after

receiving 5 years of adjuvant endocrine therapy (Pan et al., 2017). This persistent risk of breast recurrence was determined to increase at a rate of approximately 1 – 2% every year (Cuzick et al., 2010) irrespective of a patient's nodal status and stage (Pan et al., 2017). The biological mechanisms underlying the constant rate of recurrence in patients with HR+ tumors, however, are not well understood. For breast cancer patients taking aromatase inhibitors (AIs), it has been suggested that non-classical estrogens arising from androgen metabolism (Sikora et al., 2009), might explain why upwards of 20% of these patients will recur within 10 years of receiving endocrine therapy (Cuzick et al., 2010; Pan et al., 2017). Here, we further hypothesize that exposure to estrogen mimicking EDCs may also play an important role in HR+ breast cancer recurrence.

Environmental Estrogenic EDCs and Breast Cancer Risk and Progression

Mechanistically, AIs do not prevent the binding of estrogens to ER and instead work by minimizing their biological synthesis. Therefore, low concentrations of residual circulating estrogens and/or exposure to environmental estrogenic EDCs may offer another potential explanation as to why endocrine therapy fails in some breast cancer patients (Figure 1). This hypothesis is supported by epidemiological studies linking EDC exposure and breast cancer risk and poor prognosis. For instance, López-Carrillo *et al.* conducted a case-control study among women living in the northern states of Mexico and showed that exposure to diethyl phthalate was associated with an increased risk of breast cancer (Lopez-Carrillo et al., 2010). Likewise, Cohn *et al.* conducted a prospective nested case-control study in Alameda County, California, and showed that maternal exposure to the potent ER α agonist, *o,p'*-DDT, was associated with an increased risk of breast cancer among the daughters of the exposed women (Cohn et al., 2015). Palmer *et al.* conducted a follow-up cohort study and reported that prenatal exposure to diethylstilbestrol (DES), a potent nonsteroidal ER α agonist, was associated with an increased risk of breast cancer among women greater than 40 years of age (Palmer et al., 2006). Another meta-analysis of 16 studies reported a pooled odds ratio that indicated a greater risk of breast cancer from several different PCBs (Leng et al., 2016). Additionally, adipose tissue concentrations of polychlorinated biphenyls (PCBs) from nonmetastatic breast cancer patients in New York were associated with an increased risk of disease recurrence (Muscat et al., 2003).

Multiple biological mechanisms linking EDC exposure to dysregulated ER signaling have been described, including receptor agonism, antagonism, and alterations in estrogen transport and metabolism. Although many EDCs have been determined to have receptor binding affinities several order of magnitude weaker than endogenous hormones such as estrogens and androgens, the ubiquitous and chronic exposure to environmental EDCs guides much of this research (Wang et al., 2016). Here, we review the known effects relevant to ER signaling caused by exposure to multiple classes of EDCs.

Diethylstilbestrol

DES is a nonsteroidal synthetic estrogen given to women in the US between 1940 to 1970 with the intent of preventing miscarriages (Schug et al., 2016). However, in the late 1960s, several young women between the ages of 15-22, who were seen at the Massachusetts

General Hospital, were reported with clear cell adenocarcinoma of the vagina, which was previously not observed in patients under the age of 30 (Herbst and Scully, 1970; Poskanzer and Herbst, 1977). It was later determined that all of the mothers of these young women had received DES during their first trimester of pregnancy. Gestational exposure to DES is associated with a range of health issues in both sons and daughters of women exposed to DES (Schug et al., 2016). Among the daughters, infertility and reproductive tract abnormalities, such as a T-shaped uterus, were associated with maternal DES exposure (Kaufman et al., 1977; Palmer, 2001). Among the sons, DES exposure was associated with an increased likelihood for the formation of non-cancerous epididymal cysts with some inconsistent findings as whether DES exposure was associated with infertility and genital abnormalities (cryptorchidism and hypospadias) (Gill et al., 1979; Vessey et al., 1983; Wilcox et al., 1995). Unlike the other EDCs discussed below, DES has a very high affinity for ER α , estimated to be approximately 4.6 times greater than estradiol (Kuiper et al., 1997).

DDT and its Analogs

DDT and its analogs are organochlorine insecticides which were widely used from the 1940s to late 1970s for insect and malaria control (Rogan and Chen, 2005). Today, most countries have banned the use of DDT primarily over ecological concerns (Rogan and Chen, 2005). Although its common trade name is DDT, technical grade DDT typically contains a mixture of several isomers with the largest percentage of the mixture being attributed to *p,p'*-DDT (Harada et al., 2016). Some reports have found that chronic exposure to DDT has been associated with tumor formation in the liver and adverse reproductive effects in wildlife (Turusov et al., 1973; Vos et al., 2000).

Technical grade DDT contains ~15% *o,p'*-DDT, an isomer of *p,p'*-DDT, which has been shown to act as an ER α agonist in competitive receptor binding assays (Kelce et al., 1995). Data showing that *o,p'*-DDT is an ER α agonist suggests that it is a component of technical grade DDT contributing to endocrine disrupting effects observed in fish and wildlife (Harada et al., 2016; Vos et al., 2000). Due to their lipophilic nature, environmental persistence, and the reintroduction of these compounds in some parts of the world for malaria control, human exposure to DDT and its analogs remains as a topic of relevance and concern among environmental researchers (Harada et al., 2016; Rogan and Chen, 2005).

Methoxychlor

Methoxychlor is the *p,p'*-dimethoxy analog of *p,p'*-DDT that was originally intended to be a replacement for DDT due to its low acute toxicity, short biological half-life, and decreased potential for bioaccumulation (Stuchal et al., 2006). Several studies have determined that metabolites of methoxychlor are ER α agonists and likely provided a basis for its ban when it was denied reregistration by the US EPA in 2004 (Stuchal et al., 2006). Wilson *et al.* used a luciferase reporter assay to show evidence that HPTE, a metabolite of methoxychlor, binds to ER α and promotes estrogen-dependent gene activation that could be inhibited by co-treating with a potent antiestrogen (Wilson et al., 2004). Further *in vivo* data has shown that the male pups of female rats exposed to methoxychlor exhibit reduced weight of the testis, epididymis, seminal vesicles, and prostate (Chapin et al., 1997). In female pups, methoxychlor treatment lead to a mixture of estrogenic and antiestrogenic effects which

included accelerated vaginal opening, constant estrus, and atrophy of the uterus and ovaries in normal intact females (Chapin et al., 1997; Gray et al., 1989; Gray et al., 1988). In contrast, methoxychlor induced an estrogenic effect in ovariectomized female rats that was determined by an increase of uterine weight (Gray et al., 1988).

UV-filters

UV-filters are a class of chemicals that absorb a broad spectrum of UV radiation, which is why they are widely used in personal care products (PCPs) such as sunscreens, lotions, lipsticks, and creams (Dodson et al., 2012; Witorsch and Thomas, 2010). The lipophilic properties of UV-filter compounds allow them to be readily absorbed across the skin and serve as a major route of exposure in humans (Liao and Kannan, 2014; Witorsch and Thomas, 2010). Several UV-filter compounds have been shown to exhibit weak estrogenic behavior, including benzophenone-3 (BP3) which is one of the most common UV-filter compounds found in PCPs (Park et al., 2013; Schlumpf et al., 2001). *In vitro* studies have shown that UV-filter compounds BP-3, 4-methylbenzylidene camphor (4-MBC), and octyl-methoxycinnamate (OMC) can promote increased cell proliferation of estrogen-dependent MCF-7 cells and induce a uterotrophic effect in immature rats (Schlumpf et al., 2001). Wielogórska *et al.* characterized BP-3, 4-MBC, and OMC using an ERE-luciferase reporter assay and also showed evidence of weak estrogenic behavior for these three UV-filter compounds (Wielogorska et al., 2015). Interestingly, an epidemiological study reported a possible association between a metabolite of BP-3, benzophenone-1, and an increased risk of endometriosis in women (Kunisue et al., 2012). The potential relationship between UV-filter compounds with estrogen-dependent diseases such as endometriosis requires further mechanistic studies to elucidate the possible mechanisms underlying this observation.

Bisphenols

Bisphenol-A (BPA) is widely used in the manufacture of polycarbonate plastics used in bottles and toys, epoxy resins used in the lining of metal cans, and in numerous other plastic consumer products (Vandenberg et al., 2012). Several studies have provided evidence that BPA behaves as a weak estrogen and is able to bind to ER α (Delfosse et al., 2014; Delfosse et al., 2012). Naciff *et al.* studied pregnant rats and compared changes in global gene expression profiles from tissues of pups that were exposed in utero to BPA and two other ER α agonists 17 α -ethynyl estradiol (EE) and the phytoestrogen genistein (Naciff et al., 2005). They found that all three compounds significantly upregulated the same 50 ER-regulated genes which suggests BPA has a common mode of action with known ER α agonists such as EE and genistein (Naciff et al., 2005).

Murray *et al.* previously studied the relationship between the weak estrogenic behavior of BPA and its effect on mammary gland development by exposing rats to 2.5 μ g/kg BW/day of BPA during gestation (Murray et al., 2007). They found that adult rats (postnatal day 95) exposed to BPA during gestation were observed with an increase of intraductal hyperplasias in the mammary glands. Tissue sections from epithelial cells in the intraductal hyperplasias were determined by immunostaining to have significantly higher expression of ER α compared to normal mammary glands with additional evidence of increased proliferative activity. They concluded that the increased expression of ER α in the hyperplastic tissues

suggest that the proliferative activity among these cells might be driven by estrogen and that these tissues are more likely to be stimulated by estrogens later in life (Murray et al., 2007). Murray *et al.* also speculated that their findings support the hypothesis that fetal exposure to BPA and estrogen mimics may contribute to an increased risk of breast cancer later in life that might be attributed to altered mammary gland morphology. This same group conducted a similar study in nonhuman primates which were exposed to BPA during gestation and observed subtle but significant differences in morphological parameters in mammary gland density versus unexposed controls (Tharp et al., 2012). Although morphometric analysis indicated that the overall development of the mammary gland tissue was more advanced in the BPA treatment groups, immunostaining did not show evidence of increased ER α expression as reported in their earlier rodent study. Taken together, these *in vivo* findings are relevant in the context of breast cancer development in humans in light of evidence that high mammographic density is associated with an increased risk of developing breast cancer (McCormack and dos Santos Silva, 2006).

Chronic BPA exposure has also been linked to an increased risk of metastatic breast cancer in the genetically susceptible mouse mammary tumor virus (MMTV)-erbB2 overexpressing mice (Jenkins et al., 2011). Mice chronically exposed to low level BPA (2.5 and 25 μ g BPA/L drinking water) had an increased number of lung metastases relative to control animals. Low dose BPA exposure led to an increase expression of phosphorylated Akt and GSK3B. Intriguingly, similar effects were not observed at higher doses of BPA, suggesting that the relationship between BPA exposure and breast cancer progression may follow a nonmonotonic response curve (Jenkins et al., 2011).

The concern over the potential endocrine disrupting effects attributed to BPA has led to a reduction in its commercial use and the recent implementation of BPA substitutes bisphenol-S (BPS) and bisphenol-F (BPF) in numerous consumer goods (Rochester and Bolden, 2015). Interestingly, comprehensive reviews of the reported literature suggests that both BPS and BPF exhibit similar hormonal activity as BPA where they have been found to induce similar effects such as promoting an increase in uterine weight in rats (Rochester and Bolden, 2015) and activating ER α in MCF-7 cells (Mesnage et al., 2017). The widespread exposure of bisphenols and their potential endocrine disrupting effect on humans remains as current issue that warrants further investigation (Liao et al., 2012).

Parabens

Parabens, and their analogs, are alkyl esters of 4-hydroxybenzoic acid that are commonly used as preservatives in numerous consumer products including lotions, creams, cosmetics, pharmaceuticals, shampoos, sunscreens, and several other types of PCPs (Dodge et al., 2018; Dodson et al., 2012; Nishihama et al., 2016). The widespread use of parabens in PCPs has led to research studies to determine the extent of human exposure and investigate whether there is evidence for endocrine disrupting behavior (Witorsch and Thomas, 2010). *In vitro* studies have shown that parabens exhibit weak estrogenic behavior, bind to ER α to promote ER-dependent gene transcription, and induce increased cellular proliferation of ER-dependent breast cancer cells (Delfosse et al., 2014; Gonzalez et al., 2018; Watanabe et al., 2013; Wielogorska et al., 2015; Wrobel and Gregoraszczuk, 2014). Evidence of estrogenic

behavior for *n*-butylparaben *in vivo* was observed when Hu *et al.* treated immature Sprague Dawley rats at a dose of 0.16 mg/kg/day for three days via intragastric administration (Hu *et al.*, 2013). Hu *et al.* found that *n*-butylparaben was able to induce an estrogenic response in the immature rats which was assessed by an increase of uterine weight (Hu *et al.*, 2013).

Although parabens are rapidly metabolized in humans, studies have detected their presence in adipose, placental and breast tissue, as well as breast milk, serum, seminal fluid, and urine (Artacho-Cordon *et al.*, 2017; Charles and Darbre, 2013; Frederiksen *et al.*, 2011; Hines *et al.*, 2015; Honda *et al.*, 2018; Meeker *et al.*, 2011; Valle-Sistac *et al.*, 2016). A common finding among many biomonitoring studies is that urinary concentrations of parabens in women tends to be several-fold higher than in samples from men (Honda *et al.*, 2018; Moos *et al.*, 2016). Other reports suggest differential exposure among women exposed to parabens and related environmental phenols and these appear to be associated with age, race/ethnicity and geographic location (Buttke *et al.*, 2012; Calafat *et al.*, 2010; Mortensen *et al.*, 2014; Nguyen *et al.*, 2019). In men, *n*-butylparaben has been associated with markers of DNA damage in sperm (Meeker *et al.*, 2011). Similarly, reduced sperm production in male rats has been shown when they are exposed to either propylparaben or *n*-butylparaben in their diet (Oishi, 2001, 2002; Smarr *et al.*, 2018). Despite these findings, Nishihama *et al.* did not detect an association between male urinary paraben exposure and semen parameters, however, the study's small sample size may have limited the power to detect a true association (Nishihama *et al.*, 2017).

Among third trimester pregnant women, higher concentrations of parabens measured in maternal urine and cord blood were associated with an increased risk of pre-term birth, reduced birth weight, and decreased birth length (Geer *et al.*, 2017). Nishihama *et al.* provided evidence that parabens exhibit endocrine disrupting behavior when they reported a dose dependent association between paraben exposure and shorter self-reported menstrual cycle lengths among female Japanese university students (Nishihama *et al.*, 2016). Interestingly, Pollock *et al.* treated female mice with 3 mg of *n*-butylparaben by subcutaneous injection and found that urinary E2 concentrations were elevated in the mice 6 hours after the initial treatment (Pollock *et al.*, 2017). These *in vivo* findings support the human data presented by Nishihama *et al.* which suggests that parabens may influence normal reproductive function. Moreover, these data suggest paraben exposure may have additional implications in estrogen-dependent diseases such as breast cancer. For example, breast tissue concentrations of *iso*-butylparaben and *n*-butylparaben measured in patients with ER + PR+ primary breast tumors have been detected at relevant effect concentrations determined in *in vitro* studies (Charles and Darbre, 2013). For example, *iso*-butylparaben and *n*-butylparaben were measured in breast tissue samples at concentrations near their experimentally determined half maximal effective concentration (EC₅₀) or EC₃₀ respectively (Gonzalez *et al.*, 2018). However, control breast tissue samples from healthy women were not included in this study which makes it difficult to determine if weakly estrogenic compounds like parabens have a role in breast cancer or not. The ubiquitous human and wildlife (Xue and Kannan, 2016; Xue *et al.*, 2015) exposure to estrogenic paraben compounds and their associations with potentially altering estrogen regulated processes warrants further investigation.

Indirect Modulation of Estrogenic Activity by EDCs

Although paraben compounds have been reported to exhibit their estrogenic behavior by directly binding to ER α , it has been suggested that these compounds may also exert their estrogenic effects by inhibiting E2 metabolism (Prusakiewicz et al., 2007). Prusakiewicz *et al.* showed that *n*-butylparaben inhibits sulfotransferase (SULT) activity in normal human epidermal keratinocytes at low micromolar concentrations which may increase the bioavailability of non-sulfated estrogens in SULT expressing tissues. Similarly, Kester *et al.* showed that several hydroxylated polyhalogenated aromatic hydrocarbons may partially exert their estrogenic effects by inhibiting estrogen sulfotransferase SULT1E1 despite their low affinity for ER α (Kester et al., 2002). In contrast, the aryl hydrocarbon receptor agonist, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), has been shown to behave as an anti-estrogen by interfering with ER signaling (Gottel et al., 2014) which can result in the inhibition of the expression of the ER regulated gene cathepsin D (Wang et al., 2001).

Future Research Directions to Link EDC Exposure and Breast Cancer

Recurrence

Most diagnosed breast tumors express ER and cell proliferation in these tumors is induced by endogenous estrogens. Similarly, EDCs that exhibit estrogenic behavior, including some of the compounds described above, are suspected to play role in ER-dependent tumor progression. A number of potential EDCs have been detected in human breast tissue, however, human exposure to these compounds are not always associated with clinical and pathological characteristics in breast cancer (Ellsworth et al., 2015). Currently, there are a lack of studies demonstrating that exposure to EDCs is associated with an increased risk of breast cancer incidence or metathesis despite their detection in breast tissue (Charles and Darbre, 2013; Darbre et al., 2004) at biologically relevant concentrations (Gonzalez et al., 2018).

Significant gaps remain in our understanding of EDC exposure and ER+ breast cancer recurrence. First, *in vitro* and *in vivo* results suggest that many EDCs exhibit non-monotonic dose-response effects (Vandenberg et al., 2012), which have yet to be adequately captured in epidemiological studies of EDC exposure in breast cancer patients. Second, the effects of exposure to complex mixtures of EDCs are not well characterized. Recent evidence suggests that mixtures of EDCs (BPA, methylparaben, and perfluorooctanoic acid) at concentrations relevant to human exposure have synergistic effects on both normal breast and breast cancer cells (Dairkee et al., 2018). Future mechanistic work should focus on modeling the effects of chemical mixtures at doses relevant to human exposures. Third, the specific mechanisms by which EDCs could impact metastatic ER+ tumor growth are not well understood. Specifically, determining whether EDC exposure in ER+ patients promotes tumor cell dissemination (Kang and Pantel, 2013) or emergence from dormancy (Zhang et al., 2013) will be essential to define mechanistic links between EDC exposure and breast cancer recurrence. Well-designed mechanistic and epidemiological studies are needed to provide evidence whether exposure to EDCs and/or estrogen mimics contribute to breast cancer recurrence, contralateral breast cancer, or metastatic breast cancer in women receiving adjuvant endocrine therapy.

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Figure 1. Potential relationship between estrogenic EDC exposure and ER+ breast cancer recurrence.

Timeline illustrating suspected mechanism of ER+ breast tumor recurrence in the presence or absence of estrogenic EDC exposure.