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Endocrine disruption of the epigenome: a breast cancer link

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Abstract

The heritable component of breast cancer accounts for only a small proportion of total incidences. Environmental and lifestyle factors are therefore considered to among the major influencing components increasing breast cancer risk. Endocrine-disrupting chemicals (EDCs) are ubiquitous in the environment. The estrogenic property of EDCs has thus shown many associations between ongoing exposures and the development of endocrine-related diseases, including breast cancer. The environment consists of a heterogenous population of EDCs and despite many identified modes of action, including that of altering the epigenome, drawing definitive correlations regarding breast cancer has been a point of much discussion. In this review, we describe in detail well-characterized EDCs and their actions in the environment, their ability to disrupt mammary gland formation in animal and human experimental models and their associations with exposure and breast cancer risk. We also highlight the susceptibility of early-life exposure to each EDC to mediate epigenetic alterations, and where possible describe how these epigenome changes influence breast cancer risk.

Keywords

endocrine disruptors; epigenetics; breast cancer; estrogen; aromatase

Introduction

Normal growth and function of the mammary glands are dependent on the body's endocrine system. Many factors that influence breast cancer risk are therefore endocrine-associated processes, such as age at menopause, age at menarche, parity and a women's age at her first pregnancy. The significance and capacity of environmental and exogenous components, such as endocrine-disrupting chemicals (EDCs), to alter endocrine processes have resulted

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Declaration of interest

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in a greater awareness of these and breast cancer risk. An EDC is defined by the US Environmental Protection Agency as ‘an exogenous agent that interferes with synthesis, secretion, transport, metabolism, binding action, or elimination of natural blood-borne hormones that are present in the body and are responsible for homeostasis, reproduction, and developmental process’. The sources of EDCs are diverse as too are their structure and action, making prediction of their endocrine-disrupting properties a challenge. Further to this, EDCs are also a highly heterogenous set of compounds ranging from synthetic chemicals used in plastics, pesticides and pharmaceutical agents to natural chemicals found in human and animal food such as phytoestrogens.

EDCs have been shown to alter mammary development and present adverse lifelong risks in both mouse and human models (reviewed in Macon & Fenton (2013)). Originally thought to exert actions primarily through nuclear hormone receptors, such as estrogen (ERs) and progesterone receptors (PRs), research now clearly demonstrates that the mechanisms of EDCs are much broader than originally recognized. Of prominence is the growing relationship identified between EDCs altering the epigenomic landscape in cancers, including in the breast, and common diseases like cardiovascular, pulmonary or neurodegenerative disorders to name a few (Irigaray *et al.* 2007, Mathers *et al.* 2010). In such instances, early-life epigenetic programming and also those encountered during adult life are large contributing factors to overall progression of disease states (Fig. 1). Identification of epigenetic markers influenced by environmental compounds will therefore provide a potential means of early detection, prognostic value and functional information of the compound itself. This review discusses and focuses on EDCs capable of altering the epigenome, specifically those that affect endocrine-responsive organs such as the breast.

Alterations in the epigenomic landscape

The rapidly developing field of epigenetics is an exciting research area in cancer biology. The reversible nature of epigenetic changes makes it an attractive target for novel therapeutic development. Epigenetics describes a range of DNA and histone modifications that influence levels of gene expression without modifications to the underlying coding sequence (Goldberg *et al.* 2007). Such modifications include DNA methylation, histone modifications and non-coding RNAs (ncRNAs), and involve a tightly regulated network of modifying enzymes. These processes work cooperatively to facilitate gene expression control, X chromosome inactivation and genomic imprinting. The organization of DNA into chromatin structures around histones is the basis for dynamic changes that promote or suppress gene expression. Loosely packed chromatin allows for access of local transcriptional machinery for gene expression to proceed; however, tightly packed chromatin represents transcriptional repression (Li *et al.* 2007). DNA methylation and histone modifications work in tandem to determine the open or closed state of the epigenome.

DNA methylation underlies epigenetic regulation, with an inverse relationship generally observed between promoter methylation levels and gene expression. DNA methylation occurs at CpG sites, cytosine residues immediately adjacent to 5′ of guanine. CpG sites occur in clusters known as CpG islands (Ooi *et al.* 2009), and these are found in ~50% of

human gene promoters (You & Jones 2012). Hypermethylation of CpG sites within a promoter region leads to recruitment of histone-modifying enzymes to the local chromatin area to compact its structure and therefore prevent access of transcriptional machinery (Nan *et al.* 1998). Methylation of even a single CpG site may influence gene transcription, as it may interfere with the binding of transcription factors to their response elements (Demura & Bulun 2008). CpG methylation in non-promoter regions such as enhancers and introns can also alter gene expression levels (van Roon *et al.* 2011, Sandovici *et al.* 2011). DNA methylation is catalyzed by three methyltransferase enzymes: DNMT1, which is mainly responsible for the maintenance of existing DNA methylation patterns, and DNMT3a and DNMT3b, which not only establish *de novo* methylation during development but also maintain methylation patterns to a lesser degree (Hermann *et al.* 2004).

Mechanisms of DNA demethylation have more recently been uncovered, with the present model outlining both passive and active methods of demethylating CpG sites. Passive demethylation occurs when an error of methylation maintenance during replication leads to a loss of methylation on the daughter strand (Bhutani *et al.* 2011). Conversely, active demethylation is the result of a cascade of enzyme actions. Ten–Eleven Translocation (TET) proteins are initially responsible for hydroxylation of methylated cytosines (Tahiliani *et al.* 2009), following which activation-induced cytidine deaminase enzymes deaminate the DNA (Morgan *et al.* 2004). Alternatively, it has also been suggested that hydroxy-methylated DNA is not recognized by maintenance DNMTs, and therefore hydroxylation by TET proteins may lead to a loss of methylation patterns through subsequent cell cycles (He *et al.* 2011).

DNA methylation and histone modifications are intrinsically linked, working cooperatively to regulate gene expression. The recruitment of DNMTs to CpG sites may be mediated by histone modifications (Lindroth *et al.* 2004, Vire *et al.* 2006), conversely methylated CpG sites facilitate the recruitment of methyl-binding proteins to the genomic region (Boyes & Bird 1992, Bogdanovic & Veenstra 2009), which in turn recruit histone deacetylase enzymes (HDACs; Nan *et al.* 1998). Deacetylation of lysine residues on histone tails results in compaction of local chromatin structure to prevent access of transcriptional machinery and therefore repress gene transcription. To date, 18 HDAC family members have been identified and separated into class I and class II. HDACs are able to deacetylate not only histone tails but also non-histone proteins including transcription factors (Choudhary *et al.* 2009, Reichert *et al.* 2012). HDAC proteins work cooperatively with histone acetyltransferases to maintain correct histone acetylation patterns in normal cells. Histone acetyltransferases catalyze the transfer of acetyl groups from acetyl CoA to lysine residues on histone tails, resulting in an overall net reduction to chromatin compaction (Furdas *et al.* 2012).

Additional histone modifications are also critical to dictating chromatin signatures. Lysine residues may be mono-, di- or trimethylated, although this is thought to have a less direct effect on chromatin dynamics due to the nil effect this has on overall histone charge (Zentner & Henikoff 2013). Mono- or dimethylation can also occur on arginine residues, although the effect this has on nucleosomes is unclear (Bedford & Clarke 2009). Serine residues may also be phosphorylated to alter the affinity of histone-binding proteins (Hirota

et al. 2005). Other histone modifications that have been characterized to date include sumoylation, ubiquitination, ADP ribosylation (Petesch & Lis 2012) and glycosylation (Sakabe *et al.* 2010), although it is not well understood how these processes affect nucleosomes dynamics.

Small ncRNAs are also a critical component of the cell's epigenetic regulatory mechanisms. ncRNAs are broadly divided into long and short forms, with long ncRNAs generally categorized as those over 200 nucleotides in length. Long ncRNAs can be derived from gene regulatory regions, intragenic regions or mitochondrial DNA (Khalil *et al.* 2009, Hung *et al.* 2011, Rackham *et al.* 2011). They primarily act on the local genomic region from which they were derived by attracting transcription factors or other epigenetic modifying enzymes to the area. They may also serve as precursors of short ncRNAs (Wapinski & Chang 2011). Micro RNA (miRNA), endogenous siRNA and PIWI-interacting miRNA (piRNA) are the primary types of small ncRNAs found in mammalian systems (Lagos-Quintana *et al.* 2001, Kim 2006, Okamura *et al.* 2008). While they differ in their genomic origin, post-translational processing and final structure, all function to post-transcriptionally repress expression of not only their target genes but also other ncRNAs (Qureshi & Mehler 2012).

Endocrine disruption of the breast creates parallels with the epigenome

In the following sections, we describe in detail some well-characterized EDCs and their actions in the environment, ability to disrupt mammary gland formation in animal and human experimental models, and their associations with exposure and breast cancer risk. We also highlight the susceptibility to epigenetic alterations induced by early-life exposure to each EDC and where possible describe how these epigenome changes influence the risk of breast cancer. Environmental epigenetics provides direct molecular mechanisms for factors or toxicants to influence the genetic cascade of events involved in development. Critical windows of susceptibility exist where these factors modify and affect important stages of development. Generally, these critical windows are early in development when the developing organ systems are sensitive to alterations in the epigenome. Modification of the epigenome may continue throughout development, subsequently affecting the adult transcriptome and making tissues, such as the breast, susceptible to developing disease.

Importantly in mammals, exposure of gestating females to environmental factors or toxicants during the period of gonadal sex determination can alter epigenetic transgenerational inheritance. The epigenetic reprogramming and imprinting of germ cells can thus allow transgenerational transmission of adult-onset disease phenotypes. While somatic cells play critical roles in the physiology and disease states of individuals, they are not capable of transmitting information between generations. However, early-life epigenetic alterations caused by the environment may nonetheless alter somatic epigenetic stability function throughout life. The findings are summarized in Fig. 1 and Table 1.

Bisphenol A

Bisphenol A (BPA) is a commercial chemical with a high production volume that is commonly used in the manufacture of a wide variety of consumer goods. These include plastics for bottles and containers, epoxy resins that line metal food and drink cans, dental

sealants, water pipe linings and thermal paper production. Through high heat, physical manipulation or repeated use, BPA may leach from these products and unintentionally expose consumers. Oral consumption is the primary method of BPA exposure in humans, with many unknowingly ingesting contaminated food and drink. It is estimated that up to 95% of the population have detectable concentrations of BPA in their bodies (Calafat *et al.* 2005). BPA is metabolized to its glucuronidated-conjugate, and has a short half-life of ~5 h in adults (Volkel *et al.* 2002). However, in rodents at least, continued exposure results in consistently elevated serum levels of BPA (Sieli *et al.* 2011). The subject of the correlation between elevated levels of BPA in humans and increased breast cancer risk is highly topical, with no definitive studies showing an association. However, in the following sections, we discuss a number of *in vitro* and animal studies where BPA alters mammary development and epigenetic processes.

BPA acts as an estrogen mimetic and can interact with the ligand-binding domain of ERα (Sengupta *et al.* 2013), increasing cellular proliferation, potentially via reducing the rate of apoptosis (Mlynarcikova *et al.* 2013), and inducing a gene expression profile that clusters with poor breast cancer prognosis (Katchy *et al.* 2014). BPA also interacts with the orphan nuclear receptor, estrogen-related receptor γ (ERRγ; Takayanagi *et al.* 2006), and may also signal via the G-protein-coupled receptor GPER/GPR30 (Pupo *et al.* 2012). Rats and mice which are exposed prenatally to BPA show accelerated growth of the mammary gland coupled with hyperplastic epithelial ducts, more rapid development of mature structures and increased proliferation of stromal cells at an earlier age (Markey *et al.* 2001, Munoz-de-Toro *et al.* 2005, Moral *et al.* 2008, Vandenberg *et al.* 2008, Soto *et al.* 2013). Complementary studies have explored the effect of neonatal and early-life exposure to BPA on mammary gland physiology, through administration of BPA via the water supply or oral gavage (Ayyanan *et al.* 2011, Lamartiniere *et al.* 2011, Soto *et al.* 2013). This also resulted in accelerated mammary gland growth in rats and demonstrated the effects of metabolizing and accumulating BPA rather than exposure from maternal serum, where the circulating levels were not determined (Lamartiniere *et al.* 2011). Rhesus monkeys have also been studied to simulate levels of BPA exposure more physiologically relevant to humans, with similar results being obtained (Tharp *et al.* 2012). These early alterations in the mammary gland increase susceptibility of animals to 7,12-dimethylbenz[α]anthracene (DMBA)-induced mammary carcinogenesis through at least two mechanisms: molecular alteration of fetal glands without associated morphological changes and direct promotion of estrogen-dependent tumor cell growth, indicating that chronic BPA exposure may accentuate later-life risk of breast cancer development (Durando *et al.* 2007, Weber Lozada & Keri 2011).

A number of epigenetic alterations may explain the increased mammary gland proliferation and susceptibility to carcinogenesis observed in animal models. Several small studies have identified specific gene targets that are epigenetically altered in response to BPA that may increase breast epithelial proliferation and tumor development. Treatment of primary human breast epithelial cells with BPA increased DNA methylation levels in the promoter region of the gene encoding lysosomal-associated membrane protein 3, *LAMP3*, and associated decreases in mRNA expression were detected (Weng *et al.* 2010). Investigation of a panel of clinical breast cancer samples found this increase in DNA methylation to be a characteristic

of ER-positive tumors (Weng *et al.* 2010). Furthermore, *in vitro* treatment of MCF-7 ER-positive breast cancer cell lines with BPA resulted in increased expression of *EZH2*, a histone methyltransferase enzyme, which has been previously implicated in breast tumorigenesis. This resulted in an increase in histone H3 trimethylation levels, epigenetically altering the expression levels of many genes. These results translated to an *in vitro* model, as increased EZH2 activity and H3 trimethylation were also detected in the mammary glands of mice exposed to BPA *in utero* (Doherty *et al.* 2010).

Spheres of human mammary epithelial cells increased in both size and proliferation in response to BPA treatment and also showed genetic signs of senescence. Spheres treated with BPA showed increased methylation levels of key genes associated with tumor development, namely *BRCA1*, *CCNA1*, *CDKN2A*, *THBS1*, *TNFRSF10C* and *TNFRSF10D*, indicating that BPA alters the epigenome in a manner that promotes proliferation, senescence and tumor development (Qin *et al.* 2012). Additional cell line studies have demonstrated aberrant methylation of the genome resulting in upregulated DNA repair genes and downregulated pro-apoptotic genes (Fernandez *et al.* 2012), and a unique miRNA signature in BPA-treated cells distinct from miRNAs induced by estradiol (Tilghman *et al.* 2012).

Taken together, these studies to date provide clear evidence for an epigenetic component to the increased proliferation of the mammary gland and increased susceptibility to tumor development well established in animal models of BPA exposure. While a number of epigenetic targets have been implicated, the mechanisms behind BPA-induced epigenetic changes in the breast are poorly defined at present. BPA is known to increase the transcript level and activity of all three DNA methyltransferases in the brain, prostate and testes (Doshi *et al.* 2011, Tang *et al.* 2012b, Kundakovic *et al.* 2013), and establishing whether this occurs in the breast is important for understanding the mechanisms behind aberrant methylation patterns that have been observed.

Modification of EDC susceptibility by lifestyle elements such as a high-fat diet: modeling the effects of BPA

Women who immigrate from countries with low incidences of breast cancer risk to those with high incidences rapidly acquire a higher breast cancer risk within the first generation and the breast cancer incidences of their daughters and grand-daughters continue to increase to levels similar to those of residents of their new homelands (Pineda *et al.* 2001). This epidemiological observation can in part be explained by a shift of their diets from low to high fat content (a typical Western diet has over 35% fat (McKeigue *et al.* 1985)). Pregnancy is a critical window for developmental reprogramming of cancer (Walker & Ho 2012) in response to exposure to various environmental pollutants such as BPA (see above section for discussion). Since in the United States, BPA is one of the most widespread EDCs, detected in over 95% of the population (Calafat *et al.* 2008), we asked the previously unexplored question of whether a high-fat diet can modify the mammary glands' susceptibility to BPA via epigenetic modifications, and whether these findings were consistent with previous studies demonstrating the combined effects of maternal high-fat

diet and other EDCs on subsequent mammary cancer risks (Walker 1990, Luijten *et al.* 2004, Davis *et al.* 2013).

Sprague–Dawley rat dams were fed with various doses of BPA-supplemented high-fat butter diet (HFB) (2.5–2500 μg/kg body weight) during acclimation and gestation periods (Leung and Ho, unpublished data). *In utero* exposure of HFB + BPA diets did not alter i) daughter's body weight and food consumption, ii) the onset of puberty measured by time of vaginal opening, nor iii) levels of estradiol and progesterone of day-21 daughters compared with a low-fat-BPA diet. However, HFB + a low dose of BPA (25 μg/kg body weight) showed synergistic effects and caused i) a doubling of terminal end buds (TEBs) in postnatal day-21 mammary glands (these are presumed targets of carcinogenesis and this result was consistent with high-fat diets alone increasing the TEB numbers (Hilakivi-Clarke *et al.* 1998b)), ii) ERα-associated cell proliferation in the epithelial cells of these TEBs (proliferating epithelial cells are known to have low numbers of ERα-positive cells (Clarke *et al.* 1997), iii) a significant loss of 5′ hydroxymethylation of cytosine (hmC) and 5′ methylation of cytosine (mC) in the epithelial cells of the TEBs and iv) a dramatic loss of the histone H4 lysine 20 monomethylation (H4K20me1) mark in these cells (Leung and Ho, unpublished data). These early cellular and epigenetic changes correlate tightly with the dramatic increase in DMBA-induced tumor incidence from 45% in the HFB diet group to 90% in the HFB + 25 μg/kg body weight group. Importantly, these changes are non-monotonic with respect to the dose of BPA exposure exhibiting an inverted U-shape. Additionally, new data demonstrated that a high-fat butter and high-fat safflower oil diet has a greater effect than a high-fat olive oil diet in terms of promoting a response to BPA (Leung and Ho, unpublished data).

In summary, we have established an interesting animal model system to study the underpinning epigenetic mechanisms mediating the interaction between lifestyle factors and EDC exposure (Fig. 2). This has revealed the first evidence, to our knowledge, in support of the hypothesis that 'gestation is a critical window for dietary fatty acids–BPA interaction that reprograms the mammary epigenome, resulting in aberrant gene expression and increased breast cancer risk in adulthood'.

Phytoestrogens

Often referred to as 'dietary estrogens', phytoestrogens comprise a number of plant-derived xenoestrogens which function like the female sex hormone and are introduced into the body by consuming phytoestrogenic plants (Cos *et al.* 2003). Their structural similarity to estradiol means that they may exert a diverse range of estrogenic or antiestrogenic actions; however, there is some contention as to whether a diet rich in phytoestrogens is protective or detrimental to human health. Over 100 molecules have been identified as phytoestrogens, and these are broadly divided into four categories based on the chemical structure: isoflavones, lignans, coumestans and stilbens.

Phytoestrogens are able to bind differentially to both the ERα and ERβ receptors (Maggiolini *et al.* 2001, Morito *et al.* 2002), and as such their effect on breast cancer risk and development has been investigated in both epidemiological and experimental studies.

Isoflavones, namely genistein which is found in soybeans, have been a particular focus of studies, with some suggesting that the high intake of soy-based products in Asian populations may be the reason for the lower lifetime breast cancer rates compared with Caucasian American women (Lipworth *et al.* 1999). This has been substantiated in numerous epidemiological studies demonstrating that a high soy diet or supplementation reduced breast cancer risk in women (Trock *et al.* 2006). Animal studies have revealed that exposure to isoflavones, namely genistein, *in utero* through to adulthood has distinct effects on mammary development, both increasing later-life breast cancer risk (Hilakivi-Clarke *et al.* 1998a, 1999a) and protection against chemical carcinogen-induced mammary tumors (Lamartiniere *et al.* 1995, Hilakivi-Clarke *et al.* 1999b, Pei *et al.* 2003, Su *et al.* 2007). Conversely, *in vitro* studies have indicated that high doses of genistein may potentiate cell proliferation in estrogen-dependent tumors (Kao *et al.* 1998).

Clearly, the occurrence of protective or detrimental effects of isoflavones on mammary tissues may depend on the application dose and time of life. Genistein administered to pregnant dams may increase the risk of mammary cancer in female rat offspring (Hilakivi-Clarke *et al.* 1999a), whereas prepubertal exposure reduces the risk (Hilakivi-Clarke *et al.* 1999b). Furthermore, *in utero* exposure to genistein may program the mammary gland and alter susceptibility to cancer later in life (De Assis & Hilakivi-Clarke 2006), but *in utero* exposure to soy protein isolate (SPI), but not to pure genistein, protects young adult rat offspring in the *N*-nitroso-*N*-methylurea (NMU)-induced mammary carcinogenesis model (Su *et al.* 2007). Interestingly, adult-life SPI exposure also decreases the tumor incidence but elicits higher tumor grades, a feature not observed in *in utero*-exposed rats alone (Su *et al.* 2007).

A number of studies have demonstrated that phytoestrogens may play a role in altering the epigenome in the breast and other tissues. Treatment of ER-positive and ER-negative breast cancer cell lines with the isoflavones, genistein and daidzein, appears to reverse DNA hypermethylation and thus restore expression of the tumor suppressors, *BRCA1* and *BRCA2* (Bosviel *et al.* 2012). Genistein and the tomato phytoestrogen, lycopene, also show demethylating effects on the promoter region of the glutathione *S*-transferase pi-1 (*GSTP1*) gene, a tumor suppressor implicated in breast cancer development (King-Batoon *et al.* 2008). Other genes known to be targets of isoflavone-induced promoter demethylation in breast epithelial cells are *RARβ2* (*RARB*) and *CCND2* (Qin *et al.* 2009). Mechanistically, this could be through genistein repressing the expression and activity of all three DNA methyltransferase enzymes in breast cancer cells, leading to a depletion of *de novo* methylation and maintenance of DNA methylation (Li *et al.* 2009). Repression of DNMT activity is also thought to be the mechanism behind resveratrol-mediated reactivation of breast cancer-associated tumor suppressor genes (Paluszczak *et al.* 2010). Resveratrol also promotes differential binding of the methyl-binding-domain protein 2 to the promoter of *BRCA1*, preventing silencing of the gene in MCF-7 ER-positive breast cancer cells (Papoutsis *et al.* 2010).

A number of isoflavones have also been found to alter the histone methylation and acetylation signature in breast cancer cell lines (Jawaid *et al.* 2010, Dagdemir *et al.* 2013). Altered miRNA expression in response to isoflavones and resveratrol has been well

demonstrated in cancers of the prostate, pancreas and ovaries (Li *et al.* 2010, Sheth *et al.* 2012, Chiyomaru *et al.* 2013, Xu *et al.* 2013); however, there has been limited work done to elucidate miRNA regulation by phytoestrogens in the breast. In one study, miR-141 and miR-200c were upregulated by resveratrol in a mouse xenograft model to limit the population of cancer stem cells (Hagiwara *et al.* 2012). Additionally, a number of other tumor-suppressive miRNAs including miR-16 and miR-143 were upregulated by resveratrol in breast cancer cell lines (Hagiwara *et al.* 2012).

Diethylstilbestrol

Diethylstilbestrol (DES) was prescribed to millions of women up until the early 1970s, and although it has since been banned the health consequences of its use are now becoming clear in later generations. DES was used to prevent miscarriages in the first trimester, treat breast and prostate cancers, inhibit lactation, stunt the growth of rapidly growing girls and control abnormal gynecological bleeding. It was also used in the feed of chickens and cattle to accelerate growth and production of lean meat until the late 1970s (Harris & Waring 2012). All uses of DES in humans and animals were discontinued once it was established as a human carcinogen in a study linking cases of the rare vaginal clear cell carcinoma to daughters of mothers treated with DES during pregnancy (Herbst *et al.* 1971). The basis for the carcinogenic effects of DES is through its mimicking of estrogenic effects due to its design as a synthetic non-steroidal estrogen with a structure very close to that of estradiol.

In humans, DES exposure during *in utero* development has been associated with a number of later-life complications, including infertility, pregnancy complications, early menopause and cervical cancer (Hoover *et al.* 2011). A cohort study comparing women who were exposed *in utero* to DES with those born to mothers not at any stage given DES found that there was also a statistically significant increase in the risk of breast cancer development, but only for women over the age of 40. There was also an increased occurrence of breast cancer in mothers who were given DES during pregnancy, although this was not evident until decades after initial treatment (Troisi *et al.* 2007). A number of animal studies have been performed to further explore the link between DES exposure and breast cancer. Female rats born to mothers that had received injections of DES during pregnancy displayed increased rates of breast tumor incidence and tumor multiplicity both with and without chemically induced carcinogenesis with DMBA (Boylan & Calhoon 1979, Rothschild *et al.* 1987). In the mammary epithelial cell line MCF10F, DES exerts its carcinogenic effects by forming depurinating adducts with the DNA, predisposing these sites to mutations that may result in tumorigenesis (Hinrichs *et al.* 2011). Women exposed to DES *in utero*, however, lack genomic instability in normal or breast cancer tissue samples, indicating that the consequences of DES exposure may be mediated by the proliferative effects of estrogen (Larson *et al.* 2006).

Increasing evidence has implicated a role for epigenetics in DES-related mammary carcinogenesis. While there have been few studies examining epigenetic alterations by DES in mammary tissue, evidence can be drawn from other tissues in which estrogenic effects cause a predisposition to tumor development. In the mouse uterus, *Dnmt1* expression is increased with DES exposure, resulting in alterations in genome methylation patterns (Sato

et al. 2009). *Hox* genes, *Fos* and *Nsbp1* (*Hmgn5*) are among the genes with altered methylation patterns in the uterus or endometrium of animal model offspring born to mothers exposed to DES (Li *et al.* 2003, Tang *et al.* 2008, Bromer *et al.* 2009). DES increased global levels of histone H3 trimethylation by increasing the activity of the histone methyltransferase enzyme, enhancer of zeste homologue 2 (*EZH2*), in ER-positive MCF-7 breast cancer cell lines and mammary tissues of mice exposed *in utero* to DES (Doherty *et al.* 2010).

ncRNA mechanisms may also play a role in DES-mediated breast cancer development, as experimental exposure of epithelial progenitor cells to DES caused a differential expression profile in 9.1% of miRNAs screened. In particular, miR-9-3 was epigenetically silenced, and this led to promotion of cell proliferation via disordered regulation of the p53-mediated apoptotic pathway (Hsu *et al.* 2009).

Though limited evidence thus far exists to support an epigenetic basis for DES-induced breast cancer risk, studies in breast and other tissues provide a solid basis for further investigation of global epigenetic changes in the breasts of offspring exposed *in utero* to DES.

2,3,7,8-tetrachloridibenzo-*p*-dioxin

A well-known organochlorine, 2,3,7,8-tetrachloridibenzo-*p*-dioxin, or TCDD, is a pollutant byproduct of combustion and manufacture of chemicals. It has been detected in Agent Orange, the herbicide of choice for the United States Army in its bombings during the Vietnam War, thus exposing many troops and civilians to this endocrine disruptor (Kahn *et al.* 1988). Due to its long half-life of seven to eight years and its lipophilic chemical properties, TCDD tends to accumulate in both the environment and human bodies (Ogura *et al.* 2004). TCDD binds with high affinity to the aromatic hydrocarbon receptor (AhR) and is classified as an endocrine disruptor with strong anti-estrogenic properties (Jenkins *et al.* 2007).

TCDD has been associated with many adverse health consequences that have been characterized as a result of Agent Orange exposure during the Vietnam War, including congenital birth defects, pregnancy loss and increased rates of cancer (Le & Johansson 2001). As TCDD is a lipophilic compound, it has been shown to accumulate in the adipose tissue of humans, leading to a particular concern about its potential role in the promotion of breast cancer. Studies in rats have revealed that gestational and lactational exposure to TCDD resulted in permanent alterations in the development of the mammary epithelium of female offspring. These rats displayed delayed maturation of mammary structures and multiple immature undifferentiated structures, leading to an increased susceptibility to chemical-carcinogen-induced tumorigenesis (Fenton *et al.* 2002). An increase in the number of TEBs coupled with a decrease in the number of lobules of rats exposed prenatally to TCDD has also been reported (Lewis *et al.* 2001). At the molecular level, studies using a Holtzman rats model demonstrated that TCDD may be acting systemically through lower rates of estradiol production and elevation in the expression of *Esr1* mRNA in the breast, as well as in the uterus and ovaries (Chaffin *et al.* 1996).

A number of epidemiological studies have also been carried out to determine whether TCDD has a measurable impact on breast cancer risk in humans. A chemical explosion in Seveso, Italy, in 1976 resulted in exceedingly high levels of exposure to TCDD among the local residents. A retrospective study performed in 2008 examined women who were premenopausal at the time of the explosion and found that there was a measurable but not statistically significant increased prevalence of breast cancer diagnoses when compared with the general population (Warner *et al.* 2011). Similarly, female workers at a chemical pesticide plant who were occupationally exposed to high levels of TCDD showed significantly higher prevalence of breast cancer (Manuwald *et al.* 2012).

Evidence exists to indicate that TCDD has a significant effect on the epigenome in the breast and other tissues. TCDD increased association of DNMT1, histone methylation markers and methyl-binding-domain protein 2 to the promoter region of *BCRA1*, leading to hypermethylation and epigenetic silencing in breast cancer cell lines (Papoutsis *et al.* 2010). In a follow-up study by the same group, Sprague–Dawley rats treated during gestation with TCDD alone or in combination with the dietary AhR antagonist, resveratrol, increased the number of TEBs and reduced *Brca1* expression in mammary tissue of offspring, a process induced by occupancy of *Brca1* by DNMT1 and CpG methylation (Papoutsis *et al.* 2013). Interestingly, these changes were partially overridden by pre-exposure to resveratrol. In keratinocytes, TCDD is able to immortalize cell division through repression of *p53* (*Trp53*) and *p16INK4a* (*Cdkn2a*) expression. This is via promoter-methylation-mediated gene silencing, indicating that epigenetic silencing of key tumor suppressors may be a factor in breast cancer development (Ray & Swanson 2004). Both these genes and their regulatory components are known to be hypermethylated and silenced in breast cancer (Barekati *et al.* 2010, Lee *et al.* 2012), and these data indicate that TCDD may be one of the causes of epigenetic silencing and tumor development.

TCDD significantly altered the methylome in the sperm of rats three generations after *in utero* exposure. While increased breast cancer rates were not among the observed effects, increased incidence of prostate disease, polycystic ovarian disease and pubertal abnormalities was observed, indicating that endocrine mechanisms were affected by TCDD-induced methylation changes (Manikkam *et al.* 2012). *In utero* treatment of developing mouse embryos with TCDD decreased expression of the imprinted genes, *H19* and *Igf2*, through increased methylation in their promoter region. This was correlated with the increased activity of the DNA methyltransferase enzymes (Wu *et al.* 2004). miRNA regulation has been investigated as a potential mechanism for TCDD-mediated gene expression changes in the rat liver; however, no significant changes in miRNA levels were detected, indicating that TCDD does not affect the miRNA levels (Moffat *et al.* 2007).

Taken together, previous studies indicate the potential for TCDD to exert its carcinogenic effects on the breast through epigenetic mechanisms; however, more focused work needs to be done in breast tissue to expand on this hypothesis, particularly when deciphering developmental effects vs those in adults.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) are complex industrial chemicals historically used as coolants or heat-transfer agents in electrical transformers. PCBs are also used for diverse chemical applications such as plasticizers, solvents, hydraulic fluids and printing inks (reviewed in Crinnion (2011)). PCBs, although their production was banned in the USA in the late 1970s, constitute persistent organic pollutants (POPs) due to their stability, high lipophilicity and prevalence in the environment. PCBs have been found to be accumulated in breast adipose tissue (Rogan 1996, Petreas *et al.* 2011), and as a result transferred into breast milk (Dewailly *et al.* 1996). While, in recent years, a number of animal and human studies have indicated that PCBs can adversely affect thyroid functions (Salay & Garabrant 2009), epidemiological studies linking PCBs to breast cancer have been controversial with results of some studies indicating positive associations (Moysich *et al.* 1998, Dorgan *et al.* 1999, Millikan *et al.* 2000) and those of others failing to demonstrate any risk (Hoyer *et al.* 1998, Zheng *et al.* 2000, Laden *et al.* 2001). A review of the epidemiological literature examining possible links between PCB exposures and breast cancer has concluded that findings are inconsistent across studies and indicate that there is no association with increased risk (Brody *et al.* 2007, Golden & Kimbrough 2009). However, as also noted in dichlorodiphenyltrichloroethane (DDT) epidemiological studies (Cohn 2011) (discussed later in this review), the methods used in most studies do not account for exposures during earlier periods of development when mammary tissue is particularly sensitive to the toxic effects of many environmental chemicals such as PCBs (Verner *et al.* 2011).

PCBs interfere with estrogen metabolism (Korach *et al.* 1988, Connor *et al.* 1997), elevate the amount of bioavailable estradiol (Gellert 1978) and synergistically regulate estrogen-responsive genes (Jansen *et al.* 1993). *In vitro* studies of the estrogenic effects of PCBs have provided conflicting data, with some studies demonstrating an increase in breast cancer cellular proliferation and others showing no or opposing effects (Du *et al.* 2000, Bonefeld-Jorgensen *et al.* 2001, Oenga *et al.* 2004, Radice *et al.* 2008, Ptak *et al.* 2011). More recent findings have revealed roles of PCBs in breast cancer cell metastasis (Liu *et al.* 2010) and metabolism (Venkatesha *et al.* 2010).

PCBs have identified as EDCs capable of influencing epigenetic modifying processes. *In vivo* studies in rats have demonstrated that *in utero* and lactational administration of combinations of PCBs decreases the availability of the universal methyl donor *S*-adenosylmethionine (SAM), *Dnmt1* mRNA abundance and DNA methylation in liver cells (Desaulniers *et al.* 2009). It was found that PCBs decreased global genome DNA methylation and CpG methylation of the promoter of the *p16INK4a* gene (Desaulniers *et al* . 2009). The ability of PCBs to reduce DNA methylation in animals may also be reflected in humans. Two studies have revealed low levels of global DNA methylation in a population exposed to low doses of POPs (Kim *et al.* 2010) and in another in areas of the Arctic exposed to high doses (Rusiecki *et al.* 2008). The reduction in DNA methylation levels by PCBs may well be correlated with the increased transcriptional activity of target genes in breast cancer; indeed, PCBs have also found to reduce levels of H4K16Ac histone post-translational modifications (Casati *et al.* 2012), a hallmark of human cancer (Fraga *et al.* 2005). Conversely, *in utero* exposure to PCBs in rats has been shown to reduce promoter

methylation of the tumor suppressor gene *p16* (*Cdkn2a*) in hepatic cells (Desaulniers *et al.* 2009), but whether this occurs in the breast is unknown.

Obesity is a leading risk factor in the development of breast cancer, particularly in postmenopausal women where breast adipose tissue adjacent to an ER-positive tumor becomes the major source of local estrogen (Simpson *et al.* 1997). The increase in intratumoral estrogen production coincides with the elevated levels of expression and activity in breast adipose stromal cells of the aromatase gene (*CYP19A1*) (Bulun *et al.* 1993), which encodes the key enzyme involved in the conversion of androgens to estrogens. We have previously identified an inverse relationship between DNA methylation and *CYP19A1* expression in breast adipose stromal cells (Knower *et al.* 2010) and described epigenetics as a potential contributory factor in maintaining intratumoral estrogen levels in the breast (Knower *et al.* 2013). Given that PCBs accumulate in breast adipose tissue and reduce global DNA methylation, they may have a role in the sustained and increased levels of intratumoral estrogens. Indeed, there are numerous studies demonstrating that PCBs alter the expression of aromatase and other sex steroid metabolism enzymes in human (Drenth *et al.* 1998, Wojtowicz *et al.* 2005, Li 2007, Dhooge *et al.* 2011, Karmaus *et al.* 2011, Warner *et al.* 2012) and animal models (Hany *et al.* 1999, Kaya *et al.* 2002). In one instance, methylsulfonyl PCB metabolites (MeSO2-PCBs) were found to inhibit aromatase expression and activity in breast adipose fibroblasts (Heneweer *et al.* 2005). This study, however, only measured *CYP19A1* transcripts derived from the adipose-tissue-specific promoter I.4 and did not account for those derived from the breast-cancer-specific promoter II that make up 80% of the transcripts in a tumor. Whether PCBs influence sex steroid biosynthesis in the breast via epigenetic mechanisms is an area yet to be fully investigated.

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are the most widespread organic compounds found in the environment with endocrine-disrupting properties affecting hormone signaling by binding to receptors and having estrogenic properties (Santodonato 1997, Li *et al.* 2012, Sievers *et al.* 2013). PAHs are formed during the incomplete combustion of many substances including coals, crude oil, wood, gasoline, foods and cigarettes (Simon *et al.* 2008). As a consequence, higher exposures to PAHs occur among selected occupations such as firefighters and coke oven, aluminum and foundry workers (Rothman *et al.* 1993a,b, Mastrangelo *et al.* 1996). PAHs are lipophilic compounds of high stability, acting as carcinogens with genotoxic and mutagenic properties in many diseases, such as lung cancer (Boffetta *et al.* 1997). In breast, this is most reflected by the administration of the carcinogen DMBA in rodents to determine the effects of additional chemicals or alterations in gene expression transgenic models on tumor susceptibility; however, the carcinogenic properties of PAHs in human breast cancer remain unclear (Gammon & Santella 2008). Insufficient detoxification and metabolism of PAHs in the body results in the formation of PAH–DNA adducts in specific cell types (Pratt *et al.* 2011). Epidemiological studies have reported an association between PAH–DNA adducts and breast cancer incidence (Li *et al.* 1996, Rundle *et al.* 2000, Gammon *et al.* 2002, 2004). In contrast, a strong correlation between PAH–DNA adducts and breast cancer mortality was not observed (Sagiv *et al.* 2009). However, as the power of this study was limited, further investigation is warranted among larger

populations with more outcomes, particularly among premenopausal women where PAH-related mortality may be higher.

PAH exposure during early embryonic development is a critical determinant of susceptibility to epigenetic alterations. Prenatal exposure to PAHs increases PAH–DNA adducts and alters DNA methylation, mediating genespecific promoter DNA methylation changes in such instances as asthma (Perera *et al.* 2009, Tang *et al.* 2012a). In addition, findings have indicated that PAH-induced DNA adducts may preferentially form near methylated CpG sites (Denissenko *et al.* 1996, Chen *et al.* 1998, Tretyakova *et al.* 2002).

A number of studies have indicated a positive correlation between passive or active smoking and an increased breast cancer risk (Luo *et al.* 2011, Gaudet *et al.* 2013). Conflicting evidence has even indicated hormone-receptor-specific increases in risk, with separate investigations linking smoking to increased risk of developing ER-negative and ER-positive breast tumors (Manjer *et al.* 2001, Al-Delaimy *et al.* 2004). PAH chemicals found in cigarette smoke cause changes in the epigenetic landscape and, although limited evidence exists regarding breast tissues, may contribute to the increased risk of breast cancer observed in smokers. An epigenome-wide association study comparing the peripheral blood DNA methylation of smokers vs non-smokers revealed that an intergenic CpG island at the 2q37.1 locus was positively associated with breast cancer risk (Shenker *et al.* 2013), although whether PAHs are directly involved with its methylation status has not been determined. In normal human bronchial epithelial cells treated with nicotine-derived nitrosamine ketone, a chemical found in cigarette smoke, several stress-induced ncRNA transcripts were found to be upregulated. These transcripts are also upregulated in a number of breast cancer cell lines, indicating that cigarette smoke has the capacity to upregulate ncRNAs in breast cancer (Silva *et al.* 2010).

The PAH benzo[a]pyrene (BaP), mainly sourced from wood burning, but also detected in cigarettes, has been shown to have many epigenetic-disrupting properties in a number of human and animal models (Wilson & Jones 1983, Herbstman *et al.* 2012, Liang *et al.* 2012, Fang *et al.* 2013). DNA adducts involving the BaP metabolite, BaP diolepoxide (BPDE), have been identified in breast epithelial cells and human breast milk, demonstrating that BaP penetrates ductal breast epithelial cells, where most breast cancers are thought to arise (Li *et al.* 1996, Gorlewska-Roberts *et al.* 2002, Thompson *et al.* 2002). *In vitro* studies using human breast cancer cell lines have demonstrated a number of facets of BaP action, including DNA mismatch repair (Chen *et al.* 2013), cell cycle (Hamouchene *et al.* 2011), metabolism (Spink *et al.* 2008) and invasion (Miller *et al.* 2005). Epigenomic studies in breast cells reveal that the actions of BaP are widespread, altering both DNA methylation and histone patterns (Bradley *et al.* 2007, Sadikovic *et al.* 2007, Sadikovic *et al.* 2008). While BaP is an EDC with strong links to the epigenome, the various and ubiquitous exposures of PAHs in the environment should lead future work into the exploration of different combinations of PAHs and their effect on the epigenome. Furthermore, evidence needs to be generated demonstrating whether the epigenetic effects of PAHs, such as BaP, are gene-specific for breast cancer susceptibility genes. The use of *in vitro* breast cancer models is a clear starting point; however, drawing associations with epidemiological data may prove to be a difficult process.

Perfluorooctanoic acid

Perfluorooctanoic acid (PFOA) is an environmentally ubiquitous chemical that has extensive industrial applications, including in surfactants, water proofing, insulating agents and dental products (reviewed in White *et al.* (2011a)). PFOA is a non-lipophilic protein-binding chemical with a half-life of 16–22 days in mice (Lou *et al.* 2009) and 2–4 years in humans (Seals *et al.* 2011). The ongoing exposure to PFOA in the environment is reflected by its detection in the serum of animals and all humans in the US population examined (Calafat *et al.* 2007a,b). The mechanisms of action of PFOA in disease states are unclear; however, many of the affected target tissues are endocrine-regulated, such as the immune system and thyroid (White *et al.* 2011a). This is further explained by a number of studies describing interactions of PFOA with nuclear hormone receptors such as the peroxisome proliferator-activated receptor α (*PPARα* (*PPARA*)), constitutive androstane receptor (*CAR* (*NR1I3*)), pregnane X receptor (*PXR* (*NR1I2*)) and the ER, where modulation of estrogen-responsive genes has been observed (Cheng & Klaassen 2008, Rosen *et al.* 2008b, Bjork *et al.* 2011, Henry & Fair 2013).

Epidemiological studies have indicated that PFOA may be associated with a reduced risk of breast cancer as it was found to be positively associated with delayed puberty, early menopause and preeclampsia (Knox *et al.* 2011, Lopez-Espinosa *et al.* 2011, Savitz *et al.* 2012), factors that have been shown to reduce breast cancer risk (Innes & Byers 1999, Britt 2012). Recent data have however revealed a positive association between PFOA compounds and breast cancer risk in a small highly exposed Inuit population (Bonefeld-Jorgensen *et al.* 2011). More detailed examination of PFOAs in animal models revealed alterations in mammary gland development that may increase susceptibility to carcinogens. As part of these studies, prenatal PFOA exposure has been shown to delay mammary epithelial cell development, reduce ductal branching and TEB formation, increase stromal cell density, cause epithelial hyperplasia and elevate ER protein expression (White *et al.* 2007, 2009, 2011b, Zhao *et al.* 2010, Macon *et al.* 2011). The studies by White *et al.* (2011b) clearly demonstrated that the gestational and chronic adult exposure to PFOA across three generations altered mammary development. They showed that PFOA-exposed F1 dams exhibited diminished lactational morphology and reduced gland development. Of note, F2 females with chronic low-dose drinking-water exposures, at concentrations approximating those found in contaminated human water supplies, also exhibited visibly slowed mammary gland differentiation.

Limited evidence exists for PFOA in the epigenetic regulation of genes involved in breast cancer. Prenatal exposure to perfluorooctanesulfonic acid, a perfluorinated compound similar to PFOA, has been associated with Gstp1 promoter hypermethylation in rats (Wan *et al.* 2010). While *in utero* PFOA exposure has been inversely correlated with cord serum global DNA methylation in humans (Guerrero-Preston *et al.* 2010), other *in vitro* studies have indicated that PFOA does not alter global DNA methylation levels in neuroblastoma, preadipocytes, mature adipocytes or liver cells (Tian *et al.* 2012, Bastos Sales *et al.* 2013). These findings indicate that PFOA-mediated epigenetic effects may be gene-specific such as that seen on the promoter of the *GSTP* gene where hypermethylation following PFOA treatment in normal L02 liver cells is observed (Tian *et al.* 2012), a process that is also

reflected in leukemia, prostate and liver cancer cells (Zhong *et al.* 2002, Nakayama *et al.* 2004, Karius *et al.* 2011). Therefore, the gene-specific epigenetic properties of PFOA are factors to be mindful of when assessing changes in gene expression following exposure, particularly in genomic studies where large subsets of genes have been shown to be modulated in the liver and lung (Guruge *et al.* 2006, Rosen *et al.* 2007, 2008a). Analysis by high-throughput screening of the epigenome-targeting gene promoters would therefore be the best measurement of PFOA epigenetic targets. Such a study has not been conducted using mouse or human breast models, however this line of investigation worthy of pursuance.

DDT and DDE

Dichlorodiphenyltrichloroethane (DDT) is a synthetic insecticide whose long half-life, extensive use and lipophilic nature have made it a prominent environmental contaminant bioaccumulating in fat stores of animals and humans (Kelly *et al.* 2004). Despite lowering the risk of malaria and typhoid, the use of DDT was banned in 1972 due to its effects on the environment and risks to human health. The DDT metabolite, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE), continues to be detected in human serum at high concentrations (Cole *et al.* 2006). DDT and its metabolites, such as DDE, have been associated with human diseases including testicular tumors (McGlynn *et al.* 2008), type 2 diabetes (Codru *et al.* 2007), endometrial cancer (Hardell *et al.* 2004), pancreatic cancer (Porta *et al.* 2008) and breast cancer (Wolff *et al.* 1993, Safe & Zacharewski 1997). Given the strong association with endocrine-related diseases, there is no doubt that DDT acts as a strong EDC, and despite the estrogenic properties of DDT being first documented over 50 years ago (Tullner 1961), its mechanistic actions remain a point of ongoing research. Epidemiological studies using the Child Health and Development Study (CHDS) birth cohort, however, show that exposure of women exposed during pregnancy is associated with breast cancer in mothers, altered reproductive function in daughters and testicular cancer in sons, with all of these outcomes suggested as possible targets of DDT exposure (Cohn *et al.* 2003, 2007, 2010, Eskenazi *et al.* 2009).

In vitro studies have demonstrated the ability of DDT to mimic estradiol by binding to ERα and regulating breast cancer target genes (Klotz *et al.* 1996, Kuiper *et al.* 1998, Qin *et al.* 2011). DDT and its metabolites have also been shown to regulate estrogen target genes in ERa-independent mechanisms (Frigo *et al.* 2002, 2006, Bratton *et al.* 2009, 2012). The estrogenic effects of DDT and its metabolites on breast cancer have also been described for animal models. Early work provided evidence that the DDT metabolite *o,p′*-DDE enhanced mammary epithelium growth and proliferation (Brown & Lamartiniere 1995) and tumor cell proliferation (Robison *et al.* 1985). In a recent study by Johnson *et al.* (2012), HER2/Neu mice with *p,p′*-DDE metabolite implants were found to have increased mammary tumor growth; however, it was suggested that DDE exposure alone could not be the cause of tumorigenesis but rather that it is due hormonal contributions. Given that DDT metabolites are capable of increasing estrogen production through the upregulation of the aromatase gene in breast epithelial cells (Han *et al.* 2010), this is one potential mechanism for *in vivo* observations.

There have been limited investigations into the epigenetic actions of DDT and other metabolites. Of note are the findings that low doses of DDT reduce the expression of the *Dnmt1* gene in the hypothalamus of young male rats, a process correlating with global hypomethylation and demethylation of CpG islands (Shutoh *et al.* 2009). Similar observations of global hypomethylation by DDT are also found in Greenlandic Inuit populations, as discussed in the aforementioned case for PCB exposure (Rusiecki *et al.* 2008). Recent work has also emerged describing the potential for DDT to play a prominent role in miRNA regulation in the breast (Tilghman *et al.* 2012). This research identified both common and distinct microRNA profiles induced by either estradiol, BPA or DDT in MCF-7 cells, supporting the notion that although EDCs may mimic estrogenic actions, their activity differs from that of the naturally occurring steroid hormone.

The epigenetic actions of EDCs in disease states, including breast cancer, are largely dependent on early-life exposure. In the case of DDE, significant findings have associated prenatal exposure to altered steroid hormone metabolism. Focusing on the adult female offspring of the Michigan Fisheater Cohort exposed to elevated levels of organochlorines in fish consumed before or during gestation (1973–1991) (Karmaus *et al.* 2004, 2009), the expression of the genes 17-a-hydroxylase (*CYP17A1*), *CYP19A1*, and estrogen receptor α and β (*ESR1* and *ESR2*) was determined and found to be associated with prenatal exposure to DDE and PCBs and concurrent serum concentration of DDE and PCBs (Karmaus *et al.* 2011). Prenatal and concurrent DDE levels were significantly related to increased gene expression of aromatase but not of 17-a-hydroxylase, *ESR1* or *ESR2*. Given that DDT and DDE are accumulated in breast cancer adipose tissue (Ociepa-Zawal *et al.* 2010) and the fact that aromatase is under epigenetic control in the same tissue (Knower *et al.* 2010), the possibility of an epigenetic association resulting in increased intratumoral estrogen caused by DDT and it metabolites may exist. Furthermore, if future studies support those of Karmaus *et al.* (2011), gestational exposure to EDCs may result in long-term alterations in gene expression that can still be detected several decades on.

Vinclozolin

Vinclozolin, like many of the EDCs discussed already, is a lipophilic compound capable of bioaccumulating in tissues. As a pesticide it is used on fruits and vegetables to protect against several fungi, meaning that most exposure comes through the consumption of residual contamination in foods and drinking water. The endocrine-disrupting properties of vinclozolin and its metabolites were first described for the male reproductive system, where it acts as an antiandrogen (Gray *et al.* 1994, Kelce *et al.* 1994). Subsequent works have demonstrated several actions of vinclozolin as an antiandrogen, including reducing prostate weight (Monosson *et al.* 1999), modulating sex steroid levels (Quignot *et al.* 2012) and elevating the prevalence of tumors in the prostate and testis (Anway *et al.* 2006). In the female, vinclozolin exposure in rats results in the formation of mammary tumors (Anway *et al.* 2006) and disrupts mammary gland development, where epithelial branching and TEBs are increased compared with controls (El Sheikh Saad *et al.* 2011, 2013). However, very few epidemiological studies have been performed on the association of vinclozolin exposure with breast cancer.

A number of studies have been conducted, primarily by Michael Skinner and colleagues, investigating the transgenerational epigenetic effects of vinclozolin. Vinclozolin has been shown to promote an epigenetic alteration in the germ line that appears to transmit a transgenerational disease state (Anway *et al.* 2005). In this rat model, breast cancer was observed in 10% of vinclozolin-exposed F1–F4 generational rats but absent in control animals (Anway *et al.* 2006). While transcriptome profiling has been conducted on this animal model, published results are focused on male phenotypes including those of prostate cancer (Anway & Skinner 2008). Therefore, the transgenerational epigenetic targets resulting in breast tumors are yet to be fully characterized but warrant further investigation.

Concluding remarks

In this review, we have focused on EDCs that alter the epigenome and potentially alter mammary development and increase breast cancer risk. However, the health outcomes resulting from environmental exposures are highly varied and complex. The concept of defining an environmental exposure as an ‘exposome’ has recently emerged to describe the summation of all exposures and individual experiences over their lifetime, from conception to advanced age (Wild 2005). Together with the ‘inter-actome’ (e.g. genetics, epigenetics, proteomics and metabolomics), the exposome adds an additional layer of complexity to molecular epidemiological studies trying to derive associations between EDCs and common diseases, such as breast cancer. To advance the field of environmental epigenetics, future studies therefore need to consider the multiple corroborations at play. Emphasis needs to be placed on the development of animal models that mimic human diseases. In the future, such models may be advanced to the point of addressing common interactions between lifestyle factors, such as circadian rhythms, diet and physical activities, as modifiers of exposure that may yield critical information on human variability dependent on epigenetic reprogramming. The potential reversibility of epigenetics provides opportunities for the primary prevention of environmentally induced diseases. However, measuring these epigenetic changes over an individual’s lifetime will prove challenging; therefore, the development of environmental epigenetic bio-markers may be more suitable for the prediction of future disease risk, including that for breast cancer.

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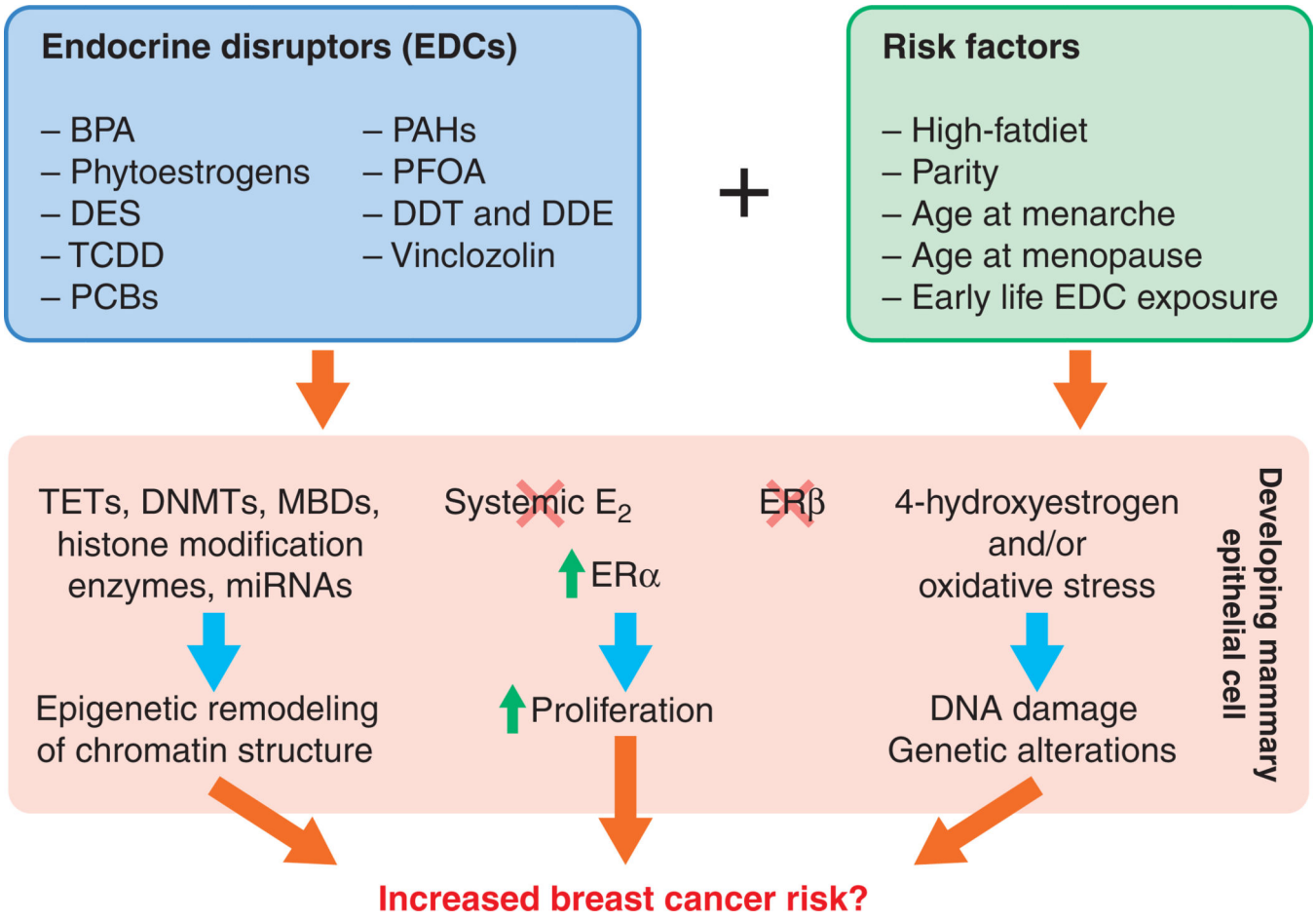

Figure 1.

Endocrine disruptors and risk factors mediate epigenome changes increasing breast cancer risk. EDC may prolong puberty and increase mammary epithelial cell proliferation allowing a longer duration or increased rate of epigenetic remodeling of the developing mammary gland leading to destabilization of chromatin integrity, mispackaging of genes in active/inactive domains and aberrant expression of genes in key regulatory pathways. The susceptibility of the action of EDCs is compounded by associated risk factors such as a high-fat diet. BPA, bisphenol A; DES, diethylstilbestrol; TCDD, 2,3,7,8-tetrachloridibenzo-*p*-dioxin; PCBs, poly-chlorinated biphenyls; PAHs, polycyclic aromatic hydrocarbons; PFOA, perfluorooctanoic acid; DDT, dichlorodiphenyltrichloroethane; DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene; TETs, Ten-Eleven Translocation proteins; DNMTs, DNA methyltransferases; MBDs, methyl-CpG-binding domain proteins; ER, estrogen receptor

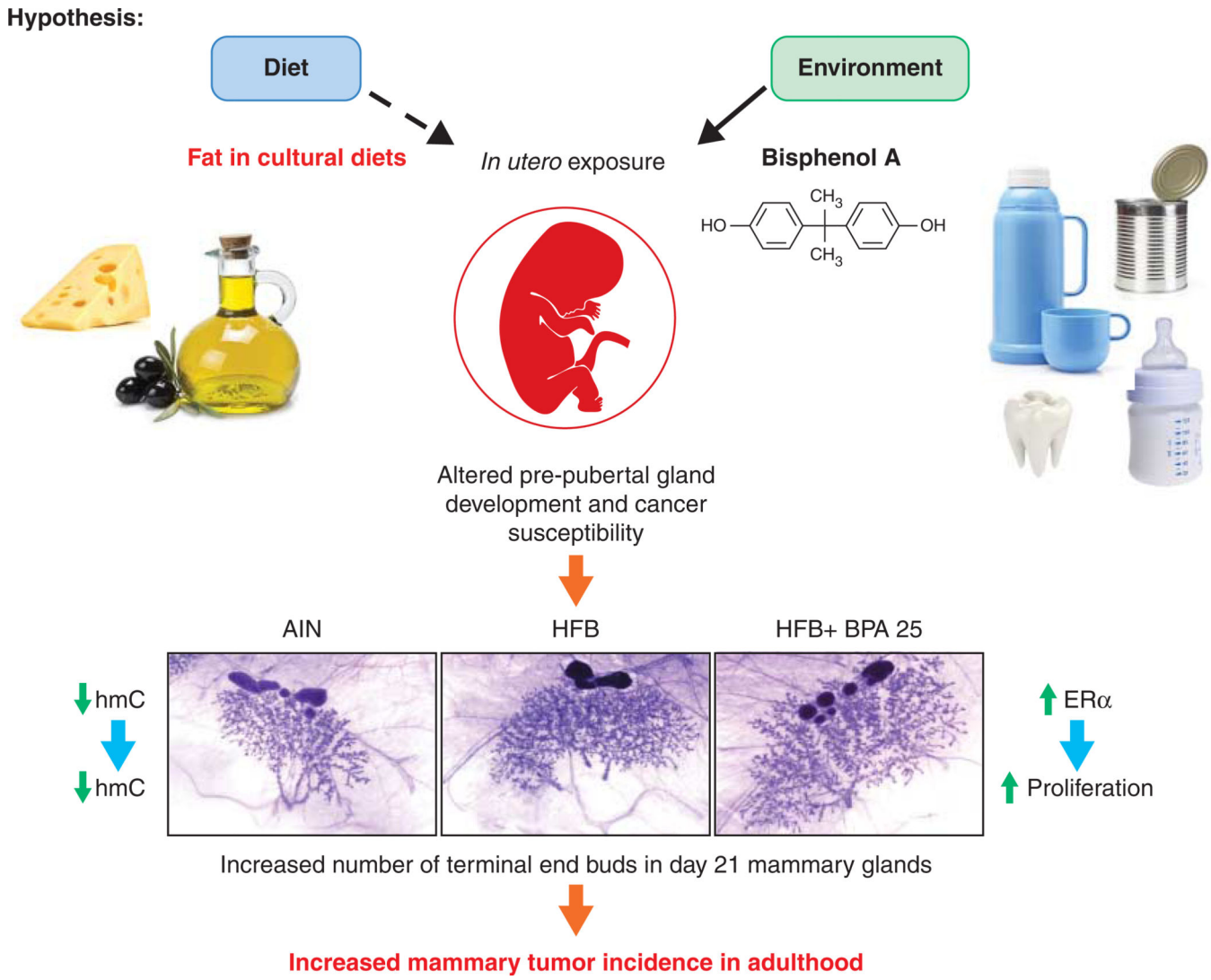

Figure 2.

Synergistic effects of *in utero* exposure to high-fat diet and BPA exposure in increasing mammary tumor incidence in adult life. The dams were fed with high-fat butter (HFB)±BPA (2.5–2500 μg/kg body weight) during acclimation and gestation periods. HFB +25 μg/kg body weight produced the maximal synergistic effects of i) the increased number of terminal end buds (TEBs), estrogen receptor α (ERα), epithelial cell proliferation, and significant loss of 5′hydroxymethylation of cytosine (hmC) and 5′ methylation of cytosine (mC) in the epithelial cells of the TEBs; and ii) increased tumor incidence in the HFB + BPA group when compared with the BPA (or the control-diet AIN).

Table 1

Summary of the epigenetic effects mediated by EDCs in breast cancer

Endocrine disruptor	Route of exposure	Breast epigenetic effect	Epigenetic effect: other tissues	References
Bisphenol A (BPA)	Plastics, dental sealants, epoxy resins, thermal paper	Altered methylation of *LAMP3, BRCA1 CCNA1, CDNK2A THBS1, TNFRSF10C* and *TNFRSF10D* Upregulation of *EZH2* Unique miRNA signature	Increase in *DNMT* activity in brain and testis	Doherty *et al.* (2010), Weng *et al.* (2010), Doshi *et al.* (2011), Qin *et al.* (2012), Tilghman *et al.* (2012) and Kundakovic *et al.* (2013)
Phytoestrogens	Plant-derived xenoestrogens (e.g. soy, tomatoes and red wine)	Demethylation of *BRCA1, BRCA2 GSTP1, RARb2 CCND2* Repression of *DNMT* activity	miRNA changes in cancers of prostate, pancreas and ovaries	King-Batoon *et al.* (2008), Li *et al.* (2009), Qin *et al.* (2009), Paluszczak *et al.* (2010) and Bosviel *et al.* (2012)
Diethylstilbestrol (DES)	Prescribed drug (discontinued 1970s)	Increase in H3 trimethylation by upregulation of *EZH2* expression	Methylation pattern of *Hox* genes, *Fos* and *Nsbp1* different in mouse uterus and endometrium *Dnmt1* expression increased in mouse uterus	Li *et al.* (2003), Tang *et al.* (2008), Bromer *et al.* (2009), Sato *et al.* (2009) and Doherty *et al.* (2010)
2,3,7,8-tetrachloridi- benzo-*p*-dioxin (TCDD)	Combustion and manufacture of chemicals	Hypermethylation of *BRCA1*	Transgenerational effects on sperm methylome Methylation-induced silencing of *p53* and *p16INK4a* in keratonites Increased *DNMT* activity in mouse embryos	Ray & Swanson (2004), Wu *et al.* (2004), Papoutsis *et al.* (2010) and Manikkam *et al.* (2012)
Polychlorinated biphenyls (PCBs)	Coolants and heat-transfer agents		Increased abundance of SAM and *DNMT*, leading to increased methylation in rat liver cells H4K16Ac post-translational histone modifications reduced	Fraga *et al.* (2005) and Desaulniers *et al.* (2009)
Polycyclic aromatic hydrocarbons (PAHs)	Incomplete combustion, including wood, cigarettes, coal and crude oil	Forms DNA adducts near methylation sites in breast epithelium and breast milk Alters DNA methylation and histone modification patterns		Li *et al.* (1996), Gorlewska-Roberts *et al.* (2002), Thompson *et al.* (2002), Bradley *et al.* (2007) and Sadikovic *et al.* (2007, 2008)

Endocrine disruptor	Route of exposure	Breast epigenetic effect	Epigenetic effect: other tissues	References
Perfluorooctanoic acid (PFOA)	Chemical in surfactants, waterproofing, insulating agents and dental products		Inverse correlation between *in utero* exposure and cord blood methylation *GSTP* hypermethylated in normal liver cells, leukemia, prostate and liver cancer cells	Zhong *et al.* (2002), Nakayama *et al.* (2004), Guerrero-Preston *et al.* (2010), Karius *et al.* (2011) and Tian *et al.* (2012)
DDT and DDE	Insecticides	Distinct miRNA signature in MCF-7 cells	Reduced expression of *Dnmt1* in rat hypothalamus	Shutoh *et al.* (2009) and Tilghman *et al.* (2012)
Vinclozolin	Pesticide		Germ line epigenetic alterations	Anway *et al.* (2006)