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Epigenetics of breast cancer: modifying role of environmental and bioactive food compounds

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Abstract

Scope—Reduced expression of tumor suppressor genes (TSG) increases the susceptibility to breast cancer. However, only a small percentage of breast tumors is related to family history and mutational inactivation of TSG. Epigenetics refers to non-mutational events that alter gene expression. Endocrine disruptors found in foods and drinking water may disrupt epigenetically hormonal regulation and increase breast cancer risk. This review centers on the working hypothesis that agonists of the aromatic hydrocarbon receptor (AHR); bisphenol A (BPA); and arsenic compounds, induce in TSG epigenetic signatures that mirror those often seen in sporadic breast tumors. Conversely, it is hypothesized that bioactive food components that target epigenetic mechanisms protect against sporadic breast cancer induced by these disruptors.

Methods and results—This review highlights 1) overlaps between epigenetic signatures placed in TSG by AHR-ligands, BPA, and arsenic with epigenetic alterations associated with sporadic breast tumorigenesis; and 2) potential opportunities for prevention of sporadic breast cancer with food components that target the epigenetic machinery.

Conclusions—Characterizing the overlap between epigenetic signatures elicited in TSG by endocrine disruptors with those observed in sporadic breast tumors may afford new strategies for breast cancer prevention with specific bioactive food components or diet.

Keywords

Epigenetics; Endocrine Disruptors; Tumor Suppressor Genes; Breast Cancer; Food Components; Cancer Prevention

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Authors contributions

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Conflict of interest

Authors have no conflict of interest.

1 Introduction

Sporadic breast tumors represent the vast majority of breast cancer cases; are not related to germline mutations in tumor suppressor genes (TSG); and usually occur later in life [1, 2]. Epigenetics refers to changes in gene expression without changes in the DNA sequence. These include alterations in DNA methylation, histone posttranslational modifications, recruitment of chromatin remodeling factors, and expression of micro (miR) and long (lncR) non-coding RNA [3]. Importantly, epigenetic modifications such as CpG methylation may be conserved through cycles of cell division and transmitted to cell progenies. The accumulation of epigenetic changes in TSG may contribute to the "cancer epigenome" in the same individual or subsequent generations even after removal of the stimuli. On the other hand, epigenetic changes are potentially reversible and, thus, offer vast opportunities for cancer therapy [4].

Sporadic tumors in which TSG are silenced often have a phenotype that mirrors that of hereditary tumors in which the same TSG is silenced through mutation. This is the case of the breast cancer susceptibility gene, *BRCA-1* whose repression through CpG methylation in sporadic breast tumors confers a "BRCAness" tumor phenotype similar to that generally seen in BRCA-1 mutation carriers [5]. Therefore, the main objective of this review was to develop a working hypothesis that endocrine disruptors induce in TSG epigenetic signatures that mirror those often seen in sporadic breast tumors. To develop this hypothesis, we focused on agonists of the aromatic hydrocarbon receptor (AHR) [2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), polycyclic aromatic hydrocarbons (PAH), polychlorinated biphenyls, and phthalates] [6]; bisphenol A (BPA) [7], and arsenic compounds[8] because they are known endocrine disruptors and ubiquitous in the environment, foods, and drinking water. Conversely, we hypothesized that food components that target the epigenetic machinery protect against alterations in TSG and mammary tumorigenesis associated with exposure to these xenobiotics. We preceded the presentation of our literature results for each xenobiotic with examples of epigenetic disruption in sporadic breast cancers of tumor suppressor proteins, miR, and lncR.

2 Methodology

We conducted a systematic review of the literature published in PubMed combining the search terms "tumor suppressor genes", "breast", "cancer", and "epigenetic", which yielded 442 articles since 1997. We also consulted the TSGene 2.0 Database (available at http://bioinfo.mc.vanderbilt.edu/TSGene/), which at the time of the access, listed 329 literature records related to breast cancer [9]. For PubMed searches of studies related to non-coding TSG, we used the terms: "breast", "cancer", "methylation", and "microRNA" or "long non-coding RNA". We followed up with a PubMed search of studies reporting on "breast", "cancer", "epigenetic" and "AHR', "BPA" or "arsenic/arsenite". Finally, we searched for studies reporting on prevention by food components of epigenetic signatures placed in TSG by AHR-ligands, BPA, and arsenic compounds in preclinical models and breast tumors. For comparison, we included examples of studies related to other endocrine-responsive tissues to further validate the role of xenobiotics as epigenetic disruptors of TSG, and prevention of sporadic tumorigenesis with food components.

3 Results

3.1 Mechanisms of epigenetic disruption of TSG in sporadic breast cancer

3.1.1 Tumor suppressor proteins—The *BRCA-1* gene is perhaps one of the best examples of a breast cancer susceptibility gene often silenced in sporadic tumors. The BRCA-1 protein is involved in transcriptional control [10, 11] and repair of DNA damage [12]. Although mutations in *BRCA-1* confer a high probability (55–65%) of developing breast cancer by age 70, germline *BRCA-1* mutations account for only a small fraction (5%–10%) of all female breast cancers, and an estimated 5%–20% of male breast tumors [13–15]. Interestingly, most breast cancers that are categorized as sporadic, have low or undetectable BRCA-1 expression in the absence of *BRCA-1* mutations [16–20]. The extent of *BRCA-1* DNA methylation in sporadic breast tumors varies from ~10 to 85% based on tumor type with higher DNA methylation usually found in more invasive, compared to lobulo-alveolar, breast tumors [21, 22]. The coincident reduced expression, and increased CpG methylation, of *BRCA-1* have also been described in earlier-onset and high-grade ovarian tumors [23–26].

The loss of BRCA-1 expression in breast tumors is almost invariably associated with reduced expression of estrogen receptor (ER)-α [27]. Familial and sporadic breast tumors with low BRCA-1 expression cluster with the basal-like and triple-negative (TNBC) phenotype with reduced expression of ERα, progesterone receptor (PR), and epidermal growth factor receptor-2 (HER-2) [5]. Interestingly, *BRCA-1*-mutation and sporadic TNBC with hypermethylated *BRCA-1* tend to be refractory to endocrine therapies based on antagonists of the ERα (i.e., tamoxifen) [12]. One mechanism contributing to antiestrogen resistance is CpG hypermethylation of *ESR1* (ERα) [28, 29], which has been documented in ~40% of breast cancer cases [30, 31], and especially, in TNBC [32]. Similarly, resistance of mammary tumors to antiprogestins has been correlated with loss of PR expression accompanied with higher expression of DNA methyltransferase (DNMT)-1 and DNMT-3b [33]. Conversely, inhibitors of DNMT [34] and histone deacetylase (HDAC) [35] enzymes were shown to favor re-expression of the ERα and PR, and restore breast cancer cells responsiveness, respectively to tamoxifen [36] and antiprogestin [33] treatment. These observations support the hypothesis that epigenetic dysregulation of tumor suppressor (i.e. *BRCA-1*) and hormone receptor (i.e. *ESR1, PGR, ERBB2*) genes combined with increased expression of DNMT contribute to sporadic breast tumorigenesis.

Posttranslational modifications of histones contribute to epigenetic dysregulation of TSG. For example, CpG hypermethylation of *RASSF1A*, *PEMT*, *SFRP*, and *RKIP* in breast tumors [9] has been linked to increased association of these genes with histone-3 trimethylated at lysine-9 (H3K9me3) and H3K27me3. These are repressive histone marks placed respectively by SUV/SET/G9 [37] and polycomb-2 enhancer of zeste-2 protein (EZH2) [38] methylases, which are associated with loss of active acetylated histone marks (i.e. H3K9Ac on *PEMT*). Conversely the combination of demethylating agents (5-aza-2'deoxycytidine) and inhibitors (i.e. GSK146) of histone methyltransferase EZH2 have been shown to restore expression of TSG and exert inhibitory effects on cell proliferation [39]. Therefore, the contribution of both DNA methylation and histone modifications should

be considered when developing models of epigenetic disruption of TSG in breast tissue [40]. This concept may be extended to other endocrine-responsive tissues such as endometrium in which tumor development and resistance to progestin therapies have been linked in ~65–85% of the cases to concurrent DNA hypermethylation of *PGR* and its association with repressive H3K27me3 mark [41].

Loss of cell cycle checkpoints compromises fidelity of DNA replication prior to cell division. One such checkpoints is p16, a cyclin-dependent kinase (CDK) inhibitor of cyclin D1 (CCND1) [42, 43]. Unlike the tumor suppressor p53, whose gene is inactivated by mutations in ~50% of all human cancers, $p16^{INK4a}$ is often silenced in breast tumors through aberrant CpG promoter methylation. Epigenetic repression of $p16^{INK4a}$ usually occurs at the early stages of sporadic breast cancer development [44], and is linked to overexpression of oncogenic CCND1. Similarly, reduced expression of p21 due to hypermethylation of the $p21/^{CIP1}$/WAF1 gene is an epigenetic alteration related to loss of cell cycle control that is observed in a large fraction (~80%) of breast tumors [45]. The hypermethylation of $p21^{CIP1/WAF1}$ and $p16^{INK4}$ have been correlated to shortening of telomeres in the breast tumor grades II and III. Telomeres are short DNA sequences present in many copies at the ends of eukaryotic chromosomes. They are essential for maintaining genomic integrity and stability [46]. Epigenetic repression of the glutathione-S-transferase-Pi (*GSTP1*) in luminal progenitor cells, is an event that has been causally linked to genomic instability and the pathogenesis of luminal-A, luminal-B, and HER-2-enriched, breast tumors [47]. Notably, reduced expression of GSTP1 has been reported in ~ 35% of breast tumor biopsies (74/215 cases) [48] in conjunction with hypermethylation of TSG (i.e. *BRCA-2, WIT-1*) and increasing grade of ductal carcinoma in situ (DCIS) [49].

3.1.2 miR and lncR—The development of sporadic breast tumors has been related, at least in part, to epigenetic dysregulation of tumor suppressor miR that bind to 3'-untranslated region (UTR) of mRNA encoding for factors that promote cancer processes [50]. For example, by targeting the 3'-UTR of *FOSL1* (FRA-1), the miR-34a/c prevents migration and invasion processes. However, expression of miR-34a/c is significantly reduced through CpG hypermethylation in metastatic breast cancer cells, and human primary breast tumors [51]. Similarly, silencing of miR-122 has been related to loss of tumor suppressor functions targeting the 3'UTR of *IGF1R*, thus leading to increased expression of insulin-like growth factor-1 receptor (IGF1R) and activation of the phosphatidylinositol 3-kinase (PI3K)/Akt/ mammalian target of rapamycin (mTOR)/p70S6K proliferative pathway [52]. In general, the development of sporadic breast cancer has been correlated to epigenetic repression of miR that activate apoptosis (miR-9-3) [53]; or inhibit proliferation (miR-148a, miR-152) [54], invasion (miR-125b) [55], metastasis (miR-126, miR-31) [56, 57]; and chemoresistance (miR-149) [58].

The concept of "BRCAness" between familial and sporadic breast tumors may be applicable to miR expression signatures. For example, silencing of members of the let-7 family (let-7a-3, let-7c, let-7e-3p) has been correlated with the development of high grade hormone receptor-negative tumors [59–61], metastasis [62], and poor outcome [63, 64]. Similarly, expression of tumor suppressor let-7a was markedly reduced in *BRCA-1* mutation carriers. These findings suggested that profiling the non-coding RNA signatures of hereditary breast

cancers [65] may provide biomarkers for the prediction of sporadic breast tumors that develop as a consequence of silencing of miR with tumor suppressor functions [66].

Risk factors for sporadic breast cancer include abnormalities in the expression of miR genes that regulate expression of DNMT. For instance, the reduced expression and CpG hypermethylation of *BRCA-1* in sporadic breast tumors has been linked to overexpression of DNMT-3b, [67], an enzyme that is in involved in de novo DNA methylation. DNMT-3b expression is under the negative control of miR-203, whose gene, however, has been shown to be silenced through CpG hypermethylated in a subset of breast cancer cell lines [68]. Therefore, the loss of post-transcriptional repression of DNMT due to silencing of tumor suppressor miR represents a mechanism that may amplify epigenetic dysregulation of TSG.

Long non-coding RNA comprise approximately 80% of all non-coding RNA [69]. Although studies of epigenetic regulation of lncR in breast cancer are somewhat limited, a recent report indicated that in breast tumors DNA methylation in lncR was more frequent than that in protein-coding genes, and associated with increased levels of H3K27me3. Interestingly, intergenic lncR comprised ~50% of the aberrantly methylated non-coding RNA promoters [70]. Therefore, silencing of lncR may help distinguishing between breast cancer patients from healthy controls. For example, the lncR *ENSG00000232821* next to *TWST1*, which encodes for a transcription factor involved in differentiation, was reported to be hypermethylated in breast tumors. Other lncR thought to have breast tumor suppressor roles include *H19*, whose aberrant hypermethylation has been described in invasive breast cancers compared with healthy breast tissue [71]. Similarly, aberrant promoter methylation of *LINC00472* was associated with decreases survival in patients with grade II breast cancer [72]. In breast cancer cells, the transcriptional repression via CpG methylation of the lncR *LED* was found to compromise the function of p53 in control of cell cycle arrest [73]. Furthermore, the epigenetic repression via CpG methylation of “host” lncR may lead to aberrant silencing of nested miR. For example, promoter hypermethylation and silencing of *LOC554202* may lead to concurrent repression of miR-31, which is transcribed from within the intronic sequence of *LOC554202*. This phenomenon has been observed in breast tumors and breast cancer cell lines of the basal-like subtype [65].

3.2 Epigenetic disruptors and breast cancer

3.2.1 AHR agonists—Agonists of the AHR are ubiquitous in the environment and include industrial xenobiotics, dietary compounds, metabolites of fatty acids, and photoproducts generated in the skin from ultraviolet radiation [74]. Studies have associated induction and/or constitutive overexpression of AHR with activation of cancer processes such as proliferation, epithelial-to-mesenchymal transition (EMT), DNA damage, inflammation, migration, angiogenesis, and metastasis; and inhibition of apoptosis [75, 76] (Figure 1). Increased AHR expression has been documented in DCIS; invasive ductal breast tumors; in conjunction with loss of p53 expression; and to a lower extent, in invasive lobular carcinomas [77]. Interestingly, some studies suggested a protective effect of AHR activation during gestation against mammary tumorigenesis later in life [78], or even discounted a role for the AHR in induction of proliferation, migration, invasion, and estrogen-dependent tumorigenesis [79]. These apparently conflicting results may be due to differences in ER

status, type of AHR agonist, and timing, duration, and dose of exposure. For example, in reproductive organs, studies with AHR agonists reported antiestrogenic effects in the presence of estrogens, and estrogenic effects in the absence of estrogens [80].

Epigenetic studies with variant human mammary epithelial cells reported that activation of the AHR was paralleled by induction of c-MYC, and EZH2; and associated with repression of miR-143/145and hypermethylation of p53-binding sites in *EPHB3* and *TRIM6*. These data suggested that AHR activation may inhibit cell cycle control via epigenetic deregulation of p53-target genes [40]. HER-2 overexpression occurs in 20–30% of breast cancers, and it has been shown to induce AHR expression via the mitogen-activated protein kinase-kinase (MEK)/extracellular-signal-regulated kinases (ERK) signaling pathways, leading to subsequent activation by the AHR without exogenous ligands, of expression of proinflammatory interleukin (IL)-6 and IL-8 [81]. The overexpression of AHR in MCF-7 cells exposed long-term to estrogen was attributed to reduced association of the *AHR* with H3K27me3 [82].

The involvement of epigenetic processes in AHR-induced tumorigenesis has been corroborated by evidence that activation of the AHR increased the expression of histone deacetylase-6 (HDAC-6) and subsequent formation of β-catenin/LEF1/TCF transcription complexes, which in turn, transactivated the *c-MYC* oncogene [83]. The aggressive proliferation of AHR-overexpressing mammary epithelial cells (i.e. MCF10AT1) was assisted by epigenetic repression via CpG methylation of *WIF-1*, which encodes an inhibitor of the Wnt pathway [84]. Conversely, depletion of AHR in ERα-negative breast cancer cells (MDA-MB-231) reduced expression of factors involved in cell growth (*MUC1, IL-8*), tryptophan metabolism (*KYNU*), multi-drug resistance (*ABCC3*), cell migration and invasion (S100A4), and angiogenesis (*VEGFA*) [85]. Our in vitro studies illustrated that the *BRCA-1* gene was a direct target for epigenetic repression by the AHR [86, 87]. These repressive effects were mediated by increased occupancy of the activated AHR and HDAC-1, and reduced association of the histone acetyltransferase (HAT) p300, SRC-1, and acetylated H4 (H4Ac), with *BRCA-1*. Other epigenetic alterations associated with AHR-mediated silencing of *BRCA-1* included deacetylation of H3K9; increased levels of H3K9me3, DNMT-1, DNMT-3a, DNMT-3b, and methyl-binding protein (MBD)-2; and CpG hypermethylation [88, 89]. Interestingly, the pattern of *BRCA-1* CpG methylation induced in AHR-treated MCF-7 cells, which harbor wild-type and hypomethylated BRCA-1 gene, was similar to the one detected in human sporadic breast tumors [4] lending support to the hypothesis that epigenetic changes induced by the AHR may play an important role in sporadic breast tumorigenesis.

In animal models, the maternal activation of the AHR impaired mammary differentiation; increased mammary terminal end bud (TEB) formation; and predisposed to chemically-induced mammary tumorigenesis in female offspring [90]. TEB are undifferentiated structures equivalent to human lobules type-1 usually found in breast tumors of *BRCA-1* mutation carriers [91]. In contrast, the knockdown of the AHR in the rodent mammary gland reduced the formation of TEB [92]. Other animal studies reported persistent impairment of mammary gland morphology in offspring as a result of gestational exposure to AHR agonists [93, 94]. Based on the information both human *BRCA-1* and rat *Brca-1* harbor

binding sites (5'-GCGTG'3') for the AHR, we extended our studies of BRCA-1 regulation to offspring of Sprague-Dawley rats treated during gestation with the AHR agonist TCDD, which increased the number of TEB in mammary tissue of offspring. These morphological changes were paralleled by greater occupancy of *Brca-1* by DNMT-1; and increased *Brca-1* hypermethylation and expression of *Ccnd1* [95]. In a follow-up study with postpubertal Sprague-Dawley rats, we found that the AHR agonist and carcinogen 7,12-dimethyl-benzo(a)anthracene (DMBA) induced mammary tumors with reduced BRCA-1 and ERα; tumors had higher *Brca-1* CpG methylation; increased expression of *AHR* and *Cyp1b1*; and higher *Ccnd1* [96].

Turning to examples of human exposure, prenatal levels of AHR-activating compounds have been correlated with delayed initiation of breast development in girls [97]. In human breast tumors, we found that TNBC had higher basal AHR expression and *BRCA-1* promoter CpG methylation compared to luminal-A, luminal-B, and HER-2-positive breast cancer tissue [96]. In human UACC-3199 cells, which harbor wild-type, but constitutively hypermethylated, *BRCA-1* [17], we confirmed that low BRCA-1 expression was mirrored by constitutive high AHR expression; conversely, the treatment with the AHR antagonist α-naphthoflavone (αNF) partially rescued BRCA-1 and ERα expression, further highlighting the potential for AHR antagonists in reactivation of *BRCA-1* in ERα-negative breast cancer cells [96].

In contrast to the large body of evidence that attributes to the AHR a causative role in sporadic breast tumorigenesis, some studies reported that activation of the AHR induced proteolytic degradation of the ERα in breast cancer MCF-7 cells [98], and hampered cell proliferation and androgen receptor (AR) expression in LNCaP prostate cancer cells [99]. The latter results were in disagreement with those of other reports indicating that the forced decrease in AHR expression through siRNA reduced by 50% growth of androgen-independent prostate cancer C4-2 cells compared to AR-positive LNCaP cells [100]. Therefore, further studies should investigate how cell context may influence the differential effects of AHR activation and/or overexpression on epigenetic control of cell proliferation in breast tissue.

3.2.2 BPA—BPA is an anthropogenic compound used in plasticizers. The leaching of BPA into food and drink containers has been attributed to its widespread detection in human urine and plasma. Estimates suggested that ~90% of total human exposure to BPA originated from foods [101]. The exposure to BPA has been correlated with increased risk of tumors of the breast and prostate [102]. Epigenetic effects of BPA have been demonstrated through decreased CpG methylation in the Agouti gene model [103]. At the cellular level, BPA can trigger changes in gene expression through nuclear pathways. BPA contains several phenolic groups and behaves as a "weak" estrogen, with 1000 to 2000-fold less affinity for the ERα. Through binding to ERα, it was shown to activate expression of proliferating cell nuclear antigen (PCNA) and cyclin A2 (CCNA2) [104–106] (Figure 2). In high-risk donor breast and T47-D (ERα-positive) epithelial cell lines, BPA (0.1 μM for 7 d) selectively increased ERα/ERβ ratio along with activation of cyclin D3 (CCND3), cdk6, CCNA, cdk2, and PCNA [107]. The induction of cell proliferation in MCF-7 cells was accompanied by activation of STAT3 [108] and CCND1, and inhibition of genes known to induce to apoptosis [109].

Bis-phenol A may induce proliferation through non-nuclear pathways involving activation of G-protein coupled receptor (GPER) [110] and ERK1/2/MAPK/Akt signals [111]. In non-cancerous human high-risk donor breast epithelial cell cells, the treatment with BPA antagonized the antiestrogenic effects of tamoxifen through activation of the PI3K/Akt/mTOR cascade [112]. MCF-7 cells exposed to BPA had increased expression of CCND1, CCNA2, and B-cell CLL/Lymphoma-2 (Bcl-2) at doses as low as 10 pM [113]. BPA-induced resistance to chemotherapeutic agents was confirmed in ERα-negative (MDA-MB-468) breast cancer cells [114]. At doses ranging from 1 to 10 μM, BPA promoted capillary permeability and angiogenesis through upregulation of vascular endothelial growth factor (VEGF) expression [115]. In ERα-negative MDA-MB-231 cells, BPA stimulated migration and invasion through activator protein-1 (AP-1), nuclear factor kappa-light-chain-enhancer in B cells (NFkB), SRC oncogene, and ERK2 pathways [116]; and EMT through inhibition of *FOXA1* and *CDH1* (E-cadherin) [117]. Repression of E-cadherin and stimulation of proliferation were observed in response to BPA, respectively in human embryonic stem [118] and normal human mammary endothelial cells [119]. These cumulative findings indicated that at levels detected in humans, BPA may elicit pleiotropic effects associated with breast cancer.

The breast tumor-inducing effects of BPA may be amplified by defects in expression of TSG. For example, primary breast cells derived from a *BRCA-1* mutation carrier produced more spherical masses in collagen and invasion when cultured in the presence of BPA [120]. Hence, women who are *BRCA* mutation carriers, i.e. have one mutated copy, or harbor one *BRCA-1* allele epigenetically-silenced, when exposed to BPA may be at greater risk of developing breast cancer. In support of this notion, primary breast cells from *BRCA-1* mutation patients were shown to form an increased number of invasive masses subsequent to BPA treatment in culture [120]. Similarly, BPA administration to *Brca-1* mutant mice was found to stimulate hyperplasia compared to control ([121].

Studies with rodent models illustrated that irrespective of timing of exposure, BPA altered mammary gland development and increased cancer risk. For example, the perinatal exposure to BPA increased the number of TEB [122] and ductal hyperplasia in offspring [123]. Moreover, the gestational, prepubertal, and pubertal exposure to BPA increased susceptibility to the AHR carcinogen, DMBA [124–128]. The prepubertal exposure to BPA induced cell proliferation and reduced p21 expression in mammary glands of Sprague-Dawley rats at postnatal day 50 [129]. The prenatal exposure to BPA was also shown to increase tumor susceptibility to nitroso-carcinogens [130], and repress immunoregulatory cytokines (IL-1, IL-2) in mammary gland of offspring [131]. In adult female rodents, BPA increased the number and size of the acini and ducts with hyperplasia of the lining epithelial cells [132]. Similar to the carcinogenic effects observed in rodent models, in nonhuman primates (rhesus monkey), the gestational exposure to BPA augmented density of mammary buds in the offspring [133].

In support of an epigenetic hypothesis for the breast cancer effects of BPA, in vitro studies with human mammary epithelial cells documented that low dose exposure (<~0.2 μM) to BPA increased DNA methylation of *BRCA-1* and $p16^{INK4}$ [120]. In MCF-7 cells, the BPA treatment increased the expression of *HOXC6*, which is commonly upregulated in breast and

prostate tumors through H3K4me3, MLL-histone methylases, and acetylation of histones associated with *HOXC6* [134]. In the non-tumorigenic breast epithelial MCF-10F cell line, BPA induced silencing through hypermethylation of proapoptotic *BCL2L11* (BIM) [119]. Studies with primary human breast epithelial cells showed that at environmentally relevant doses (4 nM), BPA induced nuclear internalization of the ERα and altered DNA methylation of *LAMP3* [135] further confirming its potential for epigenetic disruption.

In rodent models, the prenatal exposure to BPA induced H3K4me3 at the transcription initiation site of *LALBA* (alpha-lactalbumin) in the mammary gland of female offspring coincident with increased manifestation of DCIS [136]. The in utero exposure to BPA increased expression of EZH2 and H3me3 in the adult mammary gland [137]. These cumulative data supported the notion that maternal exposure to BPA may increase breast cancer risk in the offspring [138].

Changes in expression of non-coding RNA may contribute to the procarcinogenic effects of BPA. The induction of proliferation in MCF-7 cells treated with BPA was correlated to stimulation of oncogenic miR-21 [139], miR-19a and miR-19b, and repression of miR-19-related downstream targets including *PTEN* [140]. Through activation of the ERα in breast MCF-7 cells and in rat mammary tissue, BPA was found to increase expression of the lncR hox transcript antisense RNA (HOTAIR) [141], and EZH-2 [142], which have been related to epigenetic silencing and promotion of breast cancer. The in utero exposure to BPA induced in uterine tissue of offspring DNA hypomethylation of *Hoxa10* leading to increased binding of the ERα to the *Hoxa10* promoter [143] and on a genome-wide scale [144]. The treatment of human placental cell lines with BPA strongly induced miR-146a, whose abnormal expression has been linked to the development of TNBC as well as the development of cervical tumors [145, 146]. In rat models, the neonatal exposure to BPA induced the hypermethylation of *Esr1* in testis [147], and *Nsbp1* in prostate gland [148] further highlighting the contribution of epigenetic disruption in BPA-induced tumorigenesis in endocrine-responsive tissues.

3.2.3 Arsenic—Whereas chronic arsenic exposure through consumption of certain foods (i.e. rice and grains) [149, 150] and geologically contaminated water has been correlated to increased incidence of prostate cancer [151] and other malignancies [8], its impact on breast and ovarian cancer remains unclear. Common human exposure to arsenic includes inorganic trivalent arsenite (As^{III}) and pentavalent arsenate (As^{V}). However, only As^{III} has potent estrogen-like activities in connection with its affinity for the ligand-binding domain of the ERα and ability to stimulate cell growth and expression of estrogen responsive genes (i.e. *PRG*) [152] (Figure 3). Because As^{V} can be enzymatically converted to As^{III}, it may provide a reservoir of ERα-disrupting arsenic that can generate monomethylated and dimethylated metabolites, which are more toxic than the inorganic parent compounds [reviewed in 153]. Therefore, total exposure to arsenic compounds should be considered when assessing breast cancer risks. Also, sex-specific patterns of deregulation of endocrine pathways related to arsenic-contaminated drinking water suggested thresholds for total arsenic exposure may be different between males and females [154].

At the cellular level, As^{III} was shown to inhibit DNA mismatch repair leading to genomic instability [155, also reviewed in 156]. Similarly, a positive association was reported in humans between inorganic arsenic exposure in utero and oxidative/methylated DNA damage in offspring [157]. In a spontaneous mammary-tumor model (C3H/St mice), arsenic trioxide (As_2O_3) abolished the anticancer effects of selenium and increased tumor growth rates and tumor multiplicity [158]. In human fibroblasts, As_2O_3 treatment was shown to disrupt the normal function of the Fanconi/BRCA-1 DNA repair pathway and increase genomic instability [159]. Perhaps not surprisingly, women carrying certain BRCA-1 mutations (5382insC, C61G, 4153delA) were found to be at higher risk (OR ~1.25–1.7) of breast tumorigenesis associated with increased serum arsenic (~4–6 μg/L) [160].

With respect to timing of exposure, studies with a rodent model (Sprague-Dawley) demonstrated that in utero exposure to As^{III} induced an increase in the number of mammosphere-forming cells in the mammary gland of prepubertal offspring. In the postpubertal gland of offspring, the in utero exposure to As^{III} stimulated branching of epithelial cells and density, as well as overexpression of ERα, which persisted into adulthood [161]. Other investigations concluded that As^{III} was a “complete” transplacental carcinogen producing maternal dose-dependent induction of tumors of the adrenal gland, ovary, and uterus in female mice offspring [162]. Studies that examined in CD-1 mice the postnatal effects of As^{III} exposure from two weeks prior to breeding through pregnancy, lactation, after weaning, and into adulthood observed an increase in the adult incidence of tumors at doses (6 to 24 ppm in drinking water) considerably lower than those generally utilized for in utero studies [163]. The same investigators proposed that monitoring of “whole” life, rather than acute, exposure may more accurately model the risk of breast cancer in humans.

Interactions between dose and duration of exposure may impact on breast cancer risk via a biphasic mode. At low-doses (0.01–1 μM), arsenic compounds increased proliferation of non-tumorigenic MCF-10A (As_2O_3), and breast cancer MCF-7 (As^{III}) cells [164, 165]. Conversely, at higher concentrations (~5–10 μM), these compounds exerted apoptotic effects [164–166] associated with accumulation of caspase enzymes, p21, growth arrest DNA-damage-inducible-α GADD45 [167], and miR-238 [168]. These data pointed to chronic exposure as potentially important for transformation of normal breast epithelial cells, or growth of preneoplastic cells, as confirmed in prostate tissue in which As^{III} triggered the transition to a steroid hormone-independent phenotype [169].

Interactions between ER status and arsenic exposure may influence the breast cancer response. In ERα-positive (i.e. T47D, MCF-7) breast cancer cells, the treatment with As^{III} or As_2O_3 reduced the expression of ERα [170, 171]. Conversely, the treatment of ERα-negative (but ERβ positive) breast cancer MDA-MB-231 cells with As_2O_3 induced re-expression of ERα mediated by demethylation of the ERα promoter, lower expression of DMNT-1 and DNMT-3a, and partial dissociation of DNMT-1 from *ESR1* [172]. The mechanisms responsible for these differential effects of arsenic in ER-positive vs negative breast cells remain largely unknown. Importantly, in the case of ER-positive tumors, the disruption of ERα expression by arsenic may compromise the effectiveness of antiestrogen therapies.

Arsenic detoxification uses methyl groups from S-adenosyl-homocysteine (SAM), and as a result, it affects the pool of methyl groups available for DNA methylation. [153]. Methyl donors include folate, methionine, and choline. Studies with ERα-positive MCF-7 breast cancer cells showed that As^{III} treatment decreased methyl-tetrahydrofolate reductase (MTHFR) levels in a concentration-dependent fashion [166]. The reduction in MTHFR may compromise the production of methionine from homocysteine, lower SAM levels, and contribute to global DNA hypomethylation [173, 174]. Arsenic exposure through drinking was correlated with changes in global methylation of peripheral blood mononuclear cell DNA in adult populations [175]. On the other hand, preclinical [176, 177] and human [178] studies showed that arsenic induced gene-specific methylation (i.e. *p16*^{INK4}, *RASSF1*), and a decrease in telomere length associated with genomic instability [179]. Additionally, treatment with As^{III} was reported to induce cancer stem cell-like properties involving epigenetic silencing of let-7c via Ras/NF-kB pathways [180]. The maternal exposure to arsenic was also shown to alter DNA methylation in placenta [181]. Taken together, these data suggested that arsenic exposure may increase epigenetically breast cancer risk through repression of TSG involved in DNA repair and cell cycle control. In keeping with this hypothesis, our group found that in MCF-7 cells As_2O_3 (0.5–2.0 μM) and As^{III} (1.0–8.0 μM) reduced in a dose-dependent fashion BRCA-1 expression. Also, As^{III} interfered with normal development of endocrine tissues in *X. tropicalis* females (data not shown). These preliminary, albeit important, data suggest further studies are needed to clarify the epigenetic impact of arsenic compounds on TSG, and potential of dietary arsenic mimetics, for breast cancer prevention.

3.3 Prevention of epigenetic disruption with food components

This section summarizes the results of studies that reported on prevention of biochemical and epigenetic alterations commonly observed in breast tumors and associated with exposure to AHR-agonists (Figure 1), BPA (Figure 2), and arsenic (Figure 3) compounds.

3.3.1 AHR agonists

Ascorbate: In female ACI rats, ascorbate was found to prevent estrogen-induced mammary tumors and decrease oxidative stress. Specifically, vitamin C attenuated estrogen-induced markers of oxidative stress (i.e. 8-iso-prostane F2α) while inducing expression of the antioxidant enzymes superoxide dismutase and glutathione peroxidase in mammary gland tissue. Vitamin C protected against estrogen-induced mammary tumorigenesis, and increased tumor latency. The anticancer effects of ascorbate mimicked those of αNF, an inhibitor of the AHR, suggesting it could be useful for the prevention of AHR-mediated breast tumorigenesis [182]. A rodent study that evaluated the combined efficacy of α-tocopherol, selenium, and ascorbic acid on development of mammary tumors induced with DMBA, concluded that animals receiving the supplementation had lower tumor incidence and multiplicity [183]. Other studies provided evidence ascorbate may antagonize tumor progression [184] through activation of apoptosis-inducing factor-1-dependent cell death pathways [185].

Ascorbate may impact epigenetic regulation through stimulation of the catalytic activity of the Ten eleven translocation (TET) dioxygenase enzymes, and oxidation of 5-methylcytosine

(5hmc) [186] leading to demethylation and activation of TSG. The knock-out of TET functions, or overexpression of oncogenic miR-22 that represses TET expression, was shown to repress expression of miR-200 due to reduced 5hmc levels leading to increased expression of EMT genes (*BM1I*, *ZEB1/2*) [187]. Therefore, through activation of TET enzymes ascorbate may reduce the risk of cancer in mammary tissues.

Resveratrol: The phytoalexin resveratrol has received attention as a cancer preventative and antagonist of the AHR [74]. In cell culture experiments with MCF-10A cells, resveratrol (1 to 5 μM) protected against PAH-induced DNA damage by suppressing expression of CYP1A1 and CYP1B1 [188]. In studies with Sprague-Dawley rats, the supplementation in the diet starting at birth and with serum levels approaching 2.0 μM, suppressed DMBA-induced mammary cancer [189]. These protective effects of resveratrol against DMBA-induced tumorigenesis were also seen when the supplementation started later in life (45 days of age) [190], and have been attributed, at least in part, to suppression of DMBA-induced NF-kB and *PTGS2* (cyclooxygenase-2). In MCF-7 cells, at doses (1.0 μM) that approximated those achieved (2.4 μM) in human serum during pharmacokinetic studies [191], resveratrol antagonized AHR-dependent repression of *BRCA-1* transcription; deacetylation of H4 associated with *BRCA-1*; and *BRCA-1* CpG hypermethylation while reducing *BRCA-1* association of AHR, MBD-2, DNMT-1, and H3K9me3to [88, 89]. In mammary tissue of Sprague-Dawley rat female offspring, we found that the maternal supplementation with resveratrol antagonized AHR-mediated downregulation of BRCA-1 and *Brca-1* hypermethylation [95]. Conversely, resveratrol increased occupancy of *Brca-1* by the AHR repressor while lowering the recruitment of DNMT-1, the number of TEB, and expression of *Ccnd1*.

Other epigenetic changes may account for the preventative effects of resveratrol. For example, the chronic supplementation (12 wk) of resveratrol to women at increased risk of breast cancer reduced the DNA methylation of *RASSF1a* in dose-dependent fashion (50 mg > 5 mg twice daily) in mammary ductoscopy specimens, and reduced prostaglandin E2 levels in nipple aspirates [192]. Epigenetic prevention of breast cancer by resveratrol has also been linked to demethylation of the *ESR1* and sensitization to antiestrogen therapy. In cultured MDA-MB-468 cells, which are TNBC, resveratrol reduced acetylation of the oncogenic transcription factor STAT3 while increasing expression of ERα [193]. In the same study, resveratrol in combination with tamoxifen prevented growth of MDA-MD-468 tumor xenografts. Therefore, resveratrol may hold promise for epigenetic targeting of ERα-negative/AHR overexpressing breast tumors. Breast cancer protective effects of resveratrol have also been attributed to activation of tumor suppressor miR-10a/b, miR-129, miR-204, and miR-489 [194]. However, the same study documented activation by resveratrol of oncogenic miR-21. These data were in contrast with those of other reports documenting resveratrol lowered expression of miR-21 [195]. More studies are needed to clarify the impact of resveratrol on expression on non-coding RNA and relationships with breast cancer risk.

Genistein: The effects of genistein on AHR-mediated pathways may depend on cell context [196]. In Sprague-Dawley rats, the perinatal exposure from conception, through day 21, to

post-partum, was correlated with enhanced mammary gland differentiation and reduced DMBA-induced mammary tumorigenesis [197]. Similarly, the prepubertal treatment with genistein antagonized DMBA-induced mammary adenocarcinomas [198] and increased *Brca-1* expression [199]. The preventative effects of genistein against breast cancer have been related to inhibition of DNMT-1 leading to demethylation in TSG including *BRCA-1* [200], *ATM, APC, PTEN*, and *SERPINB5* [201]; enrichment of chromatin activators (H3Ac and H3K4me3) in the promoters of $p16^{INK4}$ and $p21^{CIP1/WAF1}$ [202]; and increased responsiveness to antiestrogen therapy [203].

Cruciferous indoles and isothiocyanates: Indol-3-carbinol (I3C) originates from enzymatic conversion of glucobracissin by myrosinase. Under acidic conditions, I3C undergoes rapid self-condensation to produce 3,3'-diindolylmethane (DIM). Studies concluded that I3C preferentially targeted ERα-positive breast cancer cells through the AHR and repressed proliferation [204]. The growth inhibition was dependent on BRCA-1 and BRCA-2 expression [205]. In combination with tamoxifen, I3C enhanced protection against post-initiation of mammary tumors with DMBA [206]. Similarly, DIM was reported to bind the AHR and inhibit DMBA-induced mammary tumorigenesis [207]. These data established a strong link between breast cancer prevention by I3C and DIM under conditions of AHR activation. Epigenetic prevention in prostate cancer cells by DIM, but not I3C, has been attributed to inhibition of HDAC activity accompanied by downregulation of HDAC-2, and upregulation of p21, expression [208]. Opposing effects on HDAC activity were also documented by our group in breast cancer MCF-7 cells in which the treatment with DIM (10 μM) abrogated TCDD-dependent activation of the AHR, and increased the association of AcH4, with *PTGS2* (COX-2) [209]. Anti-inflammatory properties of I3C and DIM were related to inhibition of HDAC activities [210]. DIM may prevent breast cancer through activation of miR-212/132, which in turn suppress the expression of metastatic *SOX4* [211]. Interestingly, a recent study reported that in the absence of estrogen and at concentrations commonly used in cell culture (10 μM), DIM enhanced growth of MCF-7 and T47D breast cancer cells through binding to the ERα. Conversely, at higher levels (50 μM), DIM inhibited proliferation [212]. Therefore, further studies are needed to study the bioactivity of I3C and DIM at physiological and supplemental doses and impact on epigenetic processes.

Sulforaphane (SFN) is an isothiocyanate found in cruciferous vegetables. Studies documented that SFN protected against DMBA-induced mammary tumorigenesis [213], and in MDA-MB-231 breast cancer cells and tumor xenografts it upregulated the tumor suppressor miR-140 [214]. In combination with green tea polyphenols (GTP), it reduced DNA methylation of ERα, sensitized cells to antiestrogen therapy [215], and demethylated $p21^{CIP1/WAF1}$ [216]. Also, SFN was reported to induce demethylation and expression of *PTEN* and *RARβ2* [217], and inhibit HDAC activity [218]. Surprisingly, when supplemented to B6129SF1 mice during the perinatal period, it enhanced dibenzo[def,p]chrysene (a strong AHR ligand)-dependent morbidity and lung tumorigenesis in offspring [219]. The mechanisms responsible for these pro-tumorigenic effects of DIM have not been clarified.

Green teat polyphenols include green tea catechins such as (−)-epigallocatechin-3-gallate (EGCG). In Sprague-Dawley rats treated with DMBA, green tea reduced by 87% tumors

invading the ducts [220] and preserved E-cadherin expression in DCIS lesions. These effects were attributed to EGCG, which prevented EMT, and the in vitro formation of branching structures in the presence of increased AHR expression [221]. EGCG represents ~50% of the GTP found in green tea and is an established antagonist of the AHR. It was shown to inhibit DNMT, and reactivate p16 expression (20 μM) through CpG demethylation of *p16*^{INK4a} [222]. In ERα-negative MDA-MB-231 breast cancer cells, GTP and SFN modified the chromatin structure of *ESR1* through enrichment of transcriptionally active markers (i.e. H3K9Ac) [215]. This was accompanied by reduced association of *ESR1* with SUV39H1 [3]. The combination of EGCG (20 μM) and SFN (5 μM), but not EGCG alone, was shown to reactivate ERα expression by reducing *ESR1* methylation, and [216]. These studies suggested that associations of SFN and GTP may be epigenetically more effective for breast cancer treatment than the individual compounds.

Other food components and diet: Epigenetic protection against AHR-dependent mammary tumorigenesis has been suggested for curcumin, which in MCF-7 cells repressed AHR-dependent activation of CYP1A1 and CYP1B1 [223], and increased global levels of H3K18Ac and H4K16Ac [224]. These protective effects of curcumin were confirmed in hepatocellular carcinoma cells in which it inhibited phthalate-dependent expression and activation of the AHR, migration, invasion, and EMT [225]. Similarly, antagonistic effects on the AHR were described in vitro for kaempferol, quercetin, and luteolin [196], and in the DMBA-mammary tumor model for biochanin A [197]. In a French-Canadian cohort of women carriers of a *BRCA-1* mutation, a significant reduction in incidence (~80%) of breast cancer was documented for subjects who consumed the highest intake quintile of fruits and vegetables [226]. It remains unknown if these protective effects of fruits and vegetables were related to epigenetic modulation of cancer processes. In the Nurses' Health Study, longer telomeres were observed in groups with greater adherence to the Mediterranean diet, a dietary pattern that is rich in fruits and vegetables, and monounsaturated fatty acids [227]. The intake of extra virgin olive oil, one of the main sources of fat in the Mediterranean diet, was linked to activation of *GSTP1* [228]. Interestingly, extra virgin olive oil was found to inhibit cancer-related global DNA hypomethylation [229]. Similarly, extracts from licorice, which is an herb commonly used by Mediterranean populations, were found to antagonize AHR-induced cell proliferation through induction of expression of p53 and p27. Caffeic acid was shown to demethylate miR-148 and abrogate cancer stem cell properties in MDA-MB-231 breast cancer cells [230]. These anticancer effects of caffeic acid were attributed to inhibition of AHR transactivation and nuclear localization [231]. Overall, many food components exert protective effects against epigenetic disruption induced by AHR agonists. Future studies are needed to elucidate in humans the dose- and stage of life-dependent effects of individual food components and association for breast cancer prevention.

3.3.2 BPA

Genistein: The maternal supplementation with genistein at levels consumed by populations on high-soy diet was shown to modify coat color of heterozygous viable yellow agouti (*Avy/a*) offspring toward pseudo-Agouti. This phenotypic change was correlated to increased methylation of CpG sites in a retrotransposon upstream of the transcription start site of the Agouti gene [232]. The DNA methylation induced by genistein during early

embryonic development persisted into adulthood. In the same mouse model, the maternal dietary supplementation with the methyl donor folate and genistein, prevented the aberrant transplacental hypomethylating effects of BPA [103]. Although genistein is not a methyl donor, it could epigenetically oppose tumorigenesis by antagonizing the genome-wide hypomethylating effects of BPA and other xenoestrogens, while preventing gene-specific DNA hypermethylation and histone deacetylation in TSG [233]. Genistein may protect against BPA-induced breast tumorigenesis through activation of BRCA-1 [234] and tumor suppressor miR-574-3p [235]; inhibition of oncogenic lncR HOTAIR [236], miR-34a [237], and miR-151 [238]; and modulation of DNA methylation patterns [239]. The preventative effects of genistein against BPA-induced tumorigenesis may extend to other endocrine responsive tissues such as ovary [240]. On the other hand, some reports illustrated that BPA plus genistein exerted additive effects on proliferative endpoints and expression of estrogen-target genes in MCF-7 breast cancer cells [104]. Also, genistein was shown to induce in a dose-dependent fashion (1–10 μM) VEGF secretion in MCF-7 cells [115]. Therefore, studies should clarify in preclinical models and humans populations how the combination of BPA and phytoestrogens may impact the epigenome of the breast and cancer risk.

Other food components: Flavonoids have been proposed as preventatives against breast cancer [reviewed in 241]. For example, naringenin, a citrus flavanone, and curcumin, were shown to antagonize BPA-induced proliferation of ERα-positive MCF-7 cells respectively by activating caspase-3 [242] and repressing expression of oncogenic miR19a/b [137]. The latter is a negative regulator of *PTEN*. Similarly, in ERα-positive ovarian BG-1 cancer cells, resveratrol inhibited BPA-induced proliferation through repression of ERα and CCND1 [243]. The epigenetic changes associated with these preventative effects of resveratrol in ovarian tissue await further investigation.

3.3.3. Arsenic

Folate: Folate, methionine, choline, betaine, and various B vitamins (B2, B6, and B12) are food components that regulate the pool of available methyl groups. Gestational studies of arsenic exposure in the CD-1 mouse model indicated that As^{III} induced low fetal body weight. The cotreatment with folate did not prevent these effects, but rather, induced in the offspring large changes in DNA methylation affecting CpG methylation of genes involved in Wnt-signaling [244]. The exposure to inorganic arsenic may be particularly detrimental during gestation as folate is necessary for the development of the placenta and epigenetic programming of the fetus [244]. Studies have yielded contrasting results about the effects of folate supplementation on the risk of breast cancer in women. For example, at doses higher than ~850 mg of total folate equivalents/d (DFE, 1 mg food folate=0.6 mg of supplemental folic acid), folate intake in postmenopausal women was associated with a 30% increase in the risk of breast cancer [245]. On the other hand, a study conducted also with postmenopausal women who consumed ~1,300 mg of DFE/d [246] reported a 22% reduction in the incidence of ERα-negative breast tumors. One mechanism that may influence the response to folate and arsenic is interactions with polymorphisms in the MTHFR (i.e. 677C>T), which lower the enzymatic activity of MTHFR. Women carrying mutated *BRCA-1* and the MTHFR 677TT polymorphism are at higher risk of breast and ovarian cancer compared to women expressing the wildtype *MTHFR* allele (677CC) [247].

By repressing MTHFR expression [166] and BRCA-1 function in DNA repair [159], arsenic may direct folate to DNA synthesis rather than DNA methylation, and potentiate cancer cell growth. Interestingly, breast tumors from *BRCA-1* mutation (Ser1841Asn) carriers were found to have increased expression of folate receptor-1 (*FOLR-1*), a member of the folate receptor family [248]. Protein members of the F*OLR* family have a high affinity for folic acid, and mediate delivery of 5-MTHF to the interior of cells [249]. Whereas expression of *FOLR-1* was nearly undetectable in normal cells, it increased dramatically in breast cancer and its knockout restored sensitivity to treatment with doxorubicin [250].

B12 and alcohol: Intake of B vitamins may influence the epigenetic response to arsenic. The combined action of folate and B12 may protect the one-carbon metabolic pathway and reduce arsenic-induced mutagenic DNA breaks and tissue damage [251]. On the other hand, alcohol consumption was found to exert a negative effect on breast folate availability. This was associated with $p16^{INK4}$ hypermethylation, which was enhanced in conjunction with genetic variations in methyl-transferase reductase and methylenetetrahydrofolate dehydrogenase [252]. Therefore, interactions between environmental arsenic exposure and alcohol consumption may interfere with normal folate and B12 metabolism and influence breast cancer risk through hypermethylation of TSG.

4 Conclusions

In spite of considerable progress in early cancer detection and treatment, excluding skin cancer, breast cancer remains the most common malignancy in women residing in the U.S. Because most breast cancer cases are sporadic, discovering the epigenetic mechanisms that regulate tumor development may offer new targets for prevention and treatment. These opportunities may extend to mutation carriers (e.g. BRCA-1), for whom epigenetic silencing of the wild-type allele may contribute to loss of heterozygosity and breast tumor development. Environmental pollutants, foods, and drinking water are sources of xenobiotics including agonists of the AHR (PAH, dioxin, phthalates, PCB), BPA, and arsenic which may contribute epigenetically to dysregulation of TSG and breast cancer. Conversely, some dietary compounds and patterns show promise for the prevention of breast cancers associated with these exposures. The breast cancer effects respectively of epigenetic disruptors and dietary compounds in breast tissue are influenced by complex interactions involving genotype, and timing, dose, and type (individual compound vs associations) of exposure. Future studies are needed to isolate potentially harmful interactions between epigenetic disruptors and food components in particular under supplementation regimens.

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Abbreviations

AHR	aromatic hydrocarbon receptor
αNF	αnaphthoflavone
AP-1	activator protein-1
AR	androgen receptor
As^{III}	arsenite
As^{V}	arsenate
As_2O_3	arsenic trioxide
Bcl-2	B-cell CLL/Lymphoma-2
BPA	bisphenol A
CDK	cyclin-dependent kinase
CCNA2	cyclin A2
CCND3	cyclin D3
CCND1	cyclin A1
DCIS	ductal carcinoma in situ
DFE	dietary folate equivalent
DIM	3,3'-diindolylmethane
DMBA	7,12-dimethylbenz[a]anthracene
DNMT	DNA methyltransferase
EGCG	(−)-epigallocatechin-3-gallate
EMT	epithelial-to-mesenchymal transition
ERK	extracellular-signal-regulated kinases
ER	estrogen receptor
EZH2	polycomb-2 protein enhancer of zeste
FOLR-1	folate receptor-1
GPER	G-protein coupled receptor
GTP	green tea polyphenols
GSTP1	glutathione-S-transferase-P1
HDAC	histone deacetylase

HAT	histone acetyl transferase
HER-2	epidermal growth factor receptor-2
H3K9Ac	H3 acetylated at lysine-9
H3K9me3	histone-3 trimethylated at lysine-9
H3K27me3	histone-3 trimethylated at lysine-27
H4Ac	acetylated histone-4
HOTAIR	hox transcript antisense RNA
IGFR1	insulin-like growth factor-1 receptor
I3C	indole-3-carbinol
IL	interleukin
MBD-2	methyl-binding protein-2
MEK	mitogen-activated protein kinase
MTHFR	methyl-tetrahydrofolate reductase
5-MTHF	5-methyltetrahydrofolate
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor of kappa light polypeptide gene enhancer in B-cells
PAH	polycyclic aromatic hydrocarbons
PCNA	proliferating cell nuclear antigen
PI3K	phosphatidylinositol 3-kinase
PR	progesterone receptor
SAM	S-adenosyl-homocysteine
SFN	sulforaphane
TEB	terminal end bud
TET	ten eleven translocation
TNBC	triple-negative breast cancer
TSG	tumor suppressor gene
UTR	untranslated region
VEGF	vascular endothelial growth factor

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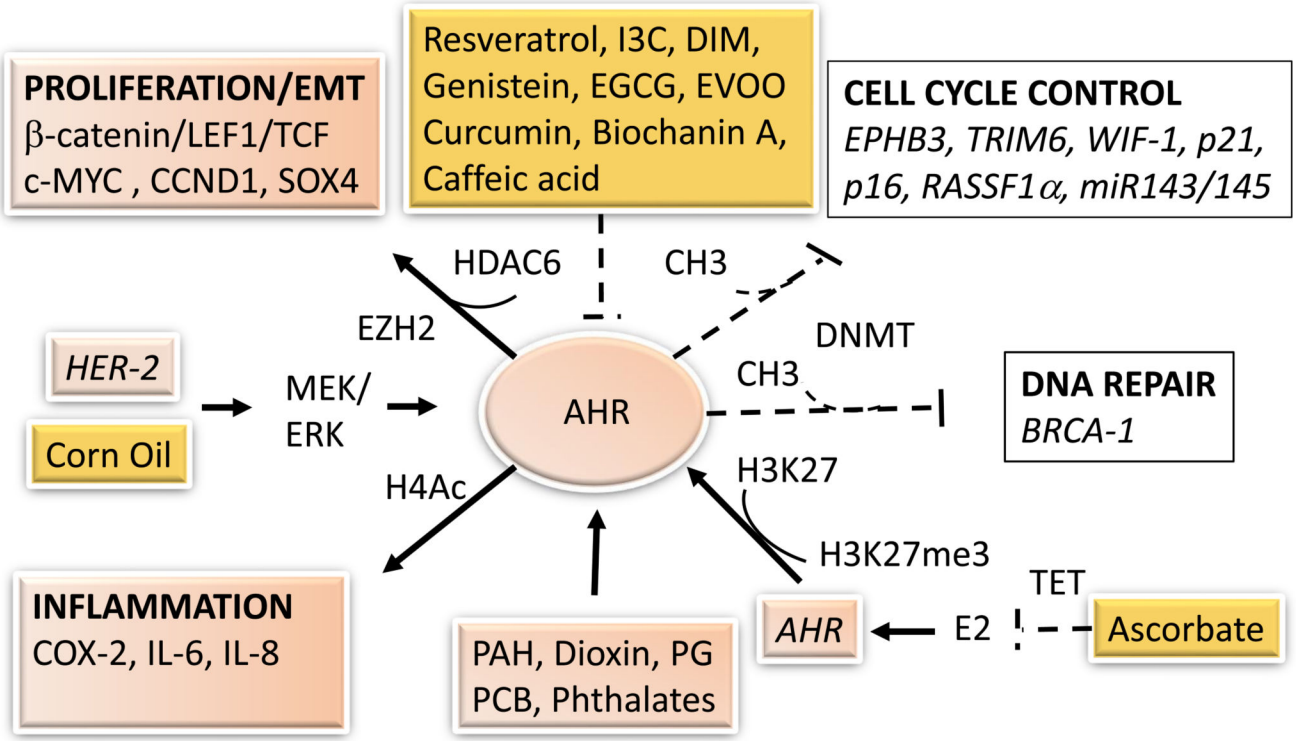

Figure 1.

Epigenetic disruption by AhR agonists and breast cancer prevention with food components. Exposure to environmental polycyclic aromatic hydrocarbons (PAH), dioxins, polychlorinated biphenyls (PCB), metabolites of fatty acids (i.e. prostaglandins, PG) activate (black solid arrows) the aromatic hydrocarbon receptor (AHR) leading to activation of proliferation, epithelial-to-mesenchymal transition (EMT), and inflammation, while disrupting cell cycle control and DNA repair tumor suppressor genes through the action of DNA methyltransferase (DNMT) enzymes. Some bioactive food components prevent (dashed back lines) AHR-induced, whereas corn oil, estrogens (E2) or overexpression of epidermal growth factor receptor-2 (HER-2) cooperate with the AHR to induce cancer processes. EVOO, extra-virgin olive oil.

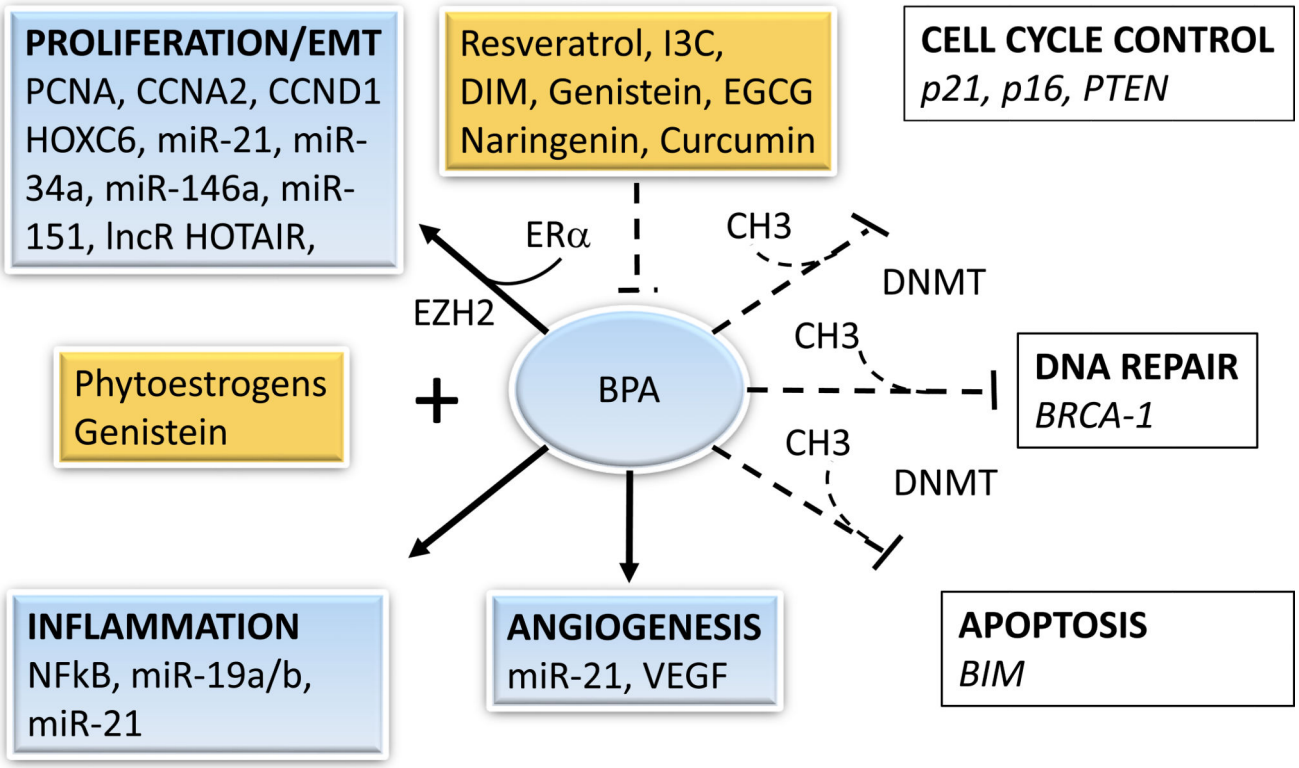

Figure 2.

Epigenetic disruption by BPA and breast cancer prevention with food components. Exposure to BPA activates (black solid arrows) factors the induce proliferation, epithelial-to-mesenchymal transition (EMT), inflammation, and angiogenesis, while silencing through DNA methyltransferases (DNMT) the expression of cell cycle control, apoptosis, and DNA repair tumor suppressor genes. Some bioactive food components prevent (dashed back lines) BPA-induced changes, whereas phytoestrogens (i.e. genistein) under certain conditions, may cooperate with BPA to induce cancer.

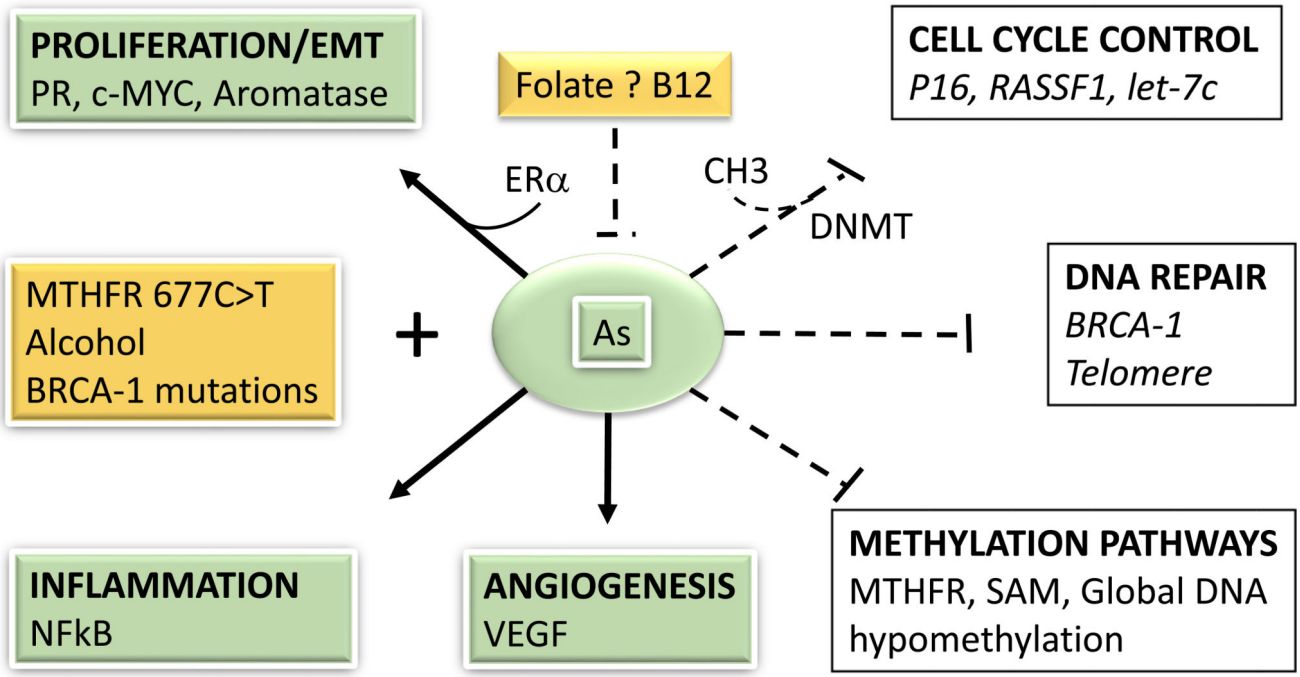

Figure 3.

Epigenetic disruption by arsenic and breast cancer prevention with food components. Exposure to arsenic (As) activates (black solid arrows) factors the induce proliferation, epithelial-to-mesenchymal transition (EMT), inflammation, and angiogenesis, while silencing through DNA methyltransferases (DNMT), the expression of cell cycle control and DNA repair tumor suppressor genes. Arsenic may deplete the pool of methyl groups (i.e. SAM) and induce global DNA hypomethylation. Some bioactive food components (i.e. folate, B12) may prevent (dashed back lines) As-induced changes, whereas others (i.e. alcohol) under certain conditions (i.e. carriers of BRCA-1 mutations or polymorphisms in the methyl-tetrahydrofolate reductase = MTHFR) may cooperate with As to induce cancer.