Review Article

Environmental contaminants in pathogenesis of breast cancer

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This review is an attempt to comprehend the diverse groups of environmental chemical contaminants with a potential for pathogenesis of breast cancer, their probable sources and the possible mechanisms by which these environmental contaminants act and interplay with other risk factors. Estrogens are closely related to the pathogenesis of breast cancer. Oxidative catabolism of estrogen, mediated by various cytochrome P450 enzymes, generates reactive free radicals that can cause oxidative damage. The same enzymes of estrogenic metabolic pathways catalyze biological activation of several environmental (xenobiotic) chemicals. Xenobiotic chemicals may exert their pathological effects through generation of reactive free radicals. Breast tissue can be a target of several xenobiotic agents. DNA-reactive metabolites of different xenobiotic compounds have been detected in breast tissue. Many phase I and II xenobiotic metabolizing enzymes are expressed in both normal and cancerous breast tissues. These enzymes play a significant role in the activation/detoxification of xenobiotic and endogenous compounds including estrogens. More than 30 carcinogenic chemicals are present in tobacco smoke; many of them are fat-soluble, resistant to metabolism and can be stored in breast adipose tissue. Similarly, pesticides are also known to cause oxidative stress; while some act as endocrine disruptor, some are shown to suppress apoptosis in estrogen sensitive cell lines. Reports have shown an association of smoking (both active and passive) and pesticides with breast cancer risk. However, the issues have remained controversial. Different mutagenic substances that are generated in the cooking process e.g., heterocyclic amines and polycyclic aromatic hydrocarbons (PAHs) can be a threat to breast tissue. PAHs and dioxins exert their adverse effects through the aryl hydrocarbon receptor (AhR), which activates several genes involved in the metabolisms of xenobiotic compounds and endogenous estrogens. These chemicals also induce AhR-dependent mitochondrial dysfunction. Many of the environmental pollutants suppress the immune system, which are implicated to risk. A better understanding about the biological effects of different environmental carcinogenic compounds and determination of their impact on rising incidence of breast cancer will be beneficial in improving preventive policy against breast cancer.

Keywords: Aryl hydrocarbon receptor, Breast cancer, Immunotoxicant, Oxidative metabolism, Xenoestrogens

Breast cancer is the most commonly occurring neoplastic disease in women worldwide and is second only to lung cancer as a cause of cancer death in women[1]. There is a gradual increase in breast cancer incidence in most developed countries and in societies which became westernized recently or are in the process. Breast cancer is the second most common cancer among Indian women; however, it is the leading cancer in Mumbai and Kolkata, and an increasing incidence has been recorded in urban females[2,3]. Among the population based cancer registries functioning in various parts of the country (India), the Mumbai Registry is a highly efficient system; and a major portion of the country's epidemiological data have been derived from Mumbai. However, aspects related with different environmental risk factors are not clear in those published reports. Studies on Mumbai population showed highest breast cancer incidence rates among Parsis and Christians, followed by Hindus and Muslims, and lowest rates among Jains and Buddhists[2,4,5]. Interestingly, data from most of the registries indicate that Christians in India have the

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greatest risk of breast cancer[6]. A more westernized lifestyle in both Christian and Parsi community is probably the reason for high incidence of breast cancer. Furthermore, higher incidence among Parsis is partly due to more consanguineous marriages (genetic etiology), a large number of spinsters or delayed marriage/first child birth and less number of children[7].

Epidemiological observations indicate a close association between the process of westernization and an increase in breast cancer incidence. Studies on the populations which migrated to the Western countries showed a higher breast cancer risk[8,9]; the phenomenon suggests an environmental influence. It is obvious that the effects of physical environment within a geographical area are more or less similar on the inhabitants; whereas lifestyle factors differ among individuals. Apart from reproduction-related factors, a westernized lifestyle is intimately associated with some particular forms of food processing/cooking practices and dietary habits such as frequent use of fast foods. In this article (under the section 'Role of food mutagens'), an attempt has been made to describe the known food related mutagens which are linked with the westernized dietary habits as well as mammary tumor development in experimental animals. The results of various epidemiological studies on different dietary factors (carcinogenic or chemopreventive) are ambiguous and conclusions have been derived mainly from the laboratory experiments. However, evidence is accumulating, which indicates an association between the westernized dietary habits and risk of breast cancer[10].

Several lines of research suggest that estrogens are closely associated with the pathological process of breast cancer. The disease risk is increased by longer duration of estrogen exposure; therefore, early menarche and/or late menopause increase the risk. Similarly, age at first pregnancy, nulliparity, obesity, estrogen replacement therapy or oral contraceptives are considered to be related with the higher risk[11,12]. Further, alcohol intake can increase risk by elevating the levels of circulating estrogen[13]. Different mechanisms may be responsible for the carcinogenicity of estrogens in the human breast such as receptor-mediated hormonal activity leading to cellular proliferation and more chances for accumulation of the genetic errors; the induction of aneuploidy by estrogen; and a cytochrome P450-mediated metabolic activation that can cause genotoxic effects. There is evidence that oxidative catabolism of estrogens, mediated by various cytochrome P450 complexes, constitutes a pathway of their metabolic activation and generates reactive free radicals that can cause oxidative stress and genomic damage[14]. There are plenty of indirect evidences to show that environmental contaminants could contribute to pathogenesis of breast cancer.

Enzymes linked with both estrogen and xenobiotic metabolisms

In the metabolism of xenobiotics (foreign chemicals), cytochrome P450s or monooxygenases perform an important function by catalyzing the hydroxylation reaction. Overall, the goal of xenobiotic metabolism is to increase the water solubility of various foreign chemicals in order to eliminate them from our physiological system; and this process occurs in two phases. Cytochrome P450 enzymes are involved in phase I reaction, which sometimes convert biologically inactive compounds into active or toxic metabolites. Subsequently, in phase II, products of phase I reaction are conjugated with various molecules such as glucuronic acid, sulfate, glutathione, acetyl or methyl groups, leading to excretion from the body. Several phase I and II enzymes are associated with estrogen metabolism (Fig. 1 and Table 1). In human breast tissue, estrogens are mainly hydroxylated by cytochrome P4501A1 (CYP1A1) and CYP1B1 into 2-hydroxyestrogens and 4-hydroxyestrogens, respectively. Higher ratio of 4-hydroxyestrogens:2-hydroxyestrogens was detected in breast cancer; and the ratio was reported to be 4:1 in breast tumor tissue extract[15,16]. It is believed that 4-hydroxyestrogens may act as a carcinogen[17].

The metabolisms of 2- and 4-hydroxyestrogens (catechol estrogens) are produced in a series of linked oxidation reactions that form the oxidative estrogen metabolism pathway[18]. Metabolism of the catechol estrogens leads to the formation of unstable semiquinone which is an intermediate in both oxidation and reduction reactions, and can react with molecular oxygen to form superoxide radicals and quinone. Superoxide radicals may be reduced to hydrogen peroxide and then, to hydroxyl radical in presence of metal ions (Fig. 2). In general, quinones can be conjugated with glutathione by glutathione-S-transferase (GST) or can form adducts with guanine and adenine base in DNA[19]. Catechol estrogen 2,3-quinone can bind stably to DNA, whereas, 3,4-quinone forms depurinating adducts with guanine and adenine, which are lost from DNA by cleavage of the glucosidic bond leaving apurinic sites with mutagenic

Table 1—Important estrogen biosynthesis/metabolism-related cytochrome P450 enzymes and their xenobiotic substrates

Enzyme	Function	Steps of catalysis	Xenobiotic substrate
CYP11A	biosynthesis	cholesterol to pregnenolone	—
CYP17 (17α-hydroxylase, C_{17-20} lyase)	biosynthesis	pregnenolone to 17α-hydroxypregnenolone to dehydroepiandrosterone (DHEA) progesterone to 17α-hydroxyprogesterone to androstenedione	—
CYP19 (aromatase)	biosynthesis	androstenedione to estrone (E1) testosterone to estradiol (E2)	—
CYP1A1	metabolism	estrogens to 2-hydroxyestrogens	PAHs
CYP1A2	metabolism	estrogens to 2-hydroxyestrogens	heterocyclic amines
CYP1B1 (4-estrogen hydroxylase)	metabolism	estrogens to 4-hydroxyestrogens	PAHs, heterocyclic amines
CYP2C9	metabolism	estrone sulfate to 16-hydroxysulfate	drug-paclitaxel
CYP3A3	metabolism	estrogens to 2-hydroxyestrogens	—
CYP3A4	metabolism	estrogens to 2- and 16-hydroxyestrogens	PAHs, aflatoxin
CYP3A5	metabolism	estrogens to 16α-hydroxyestrogens	paclitaxel, vinca alkaloids, tamoxifen

PAHs – polycyclic aromatic hydrocarbons
(N.B.: CYP is 'cytochrome P450 enzyme', the next numeral indicates the 'family'; the capital letter denotes the 'subfamily', and the last number designates the individual 'member')
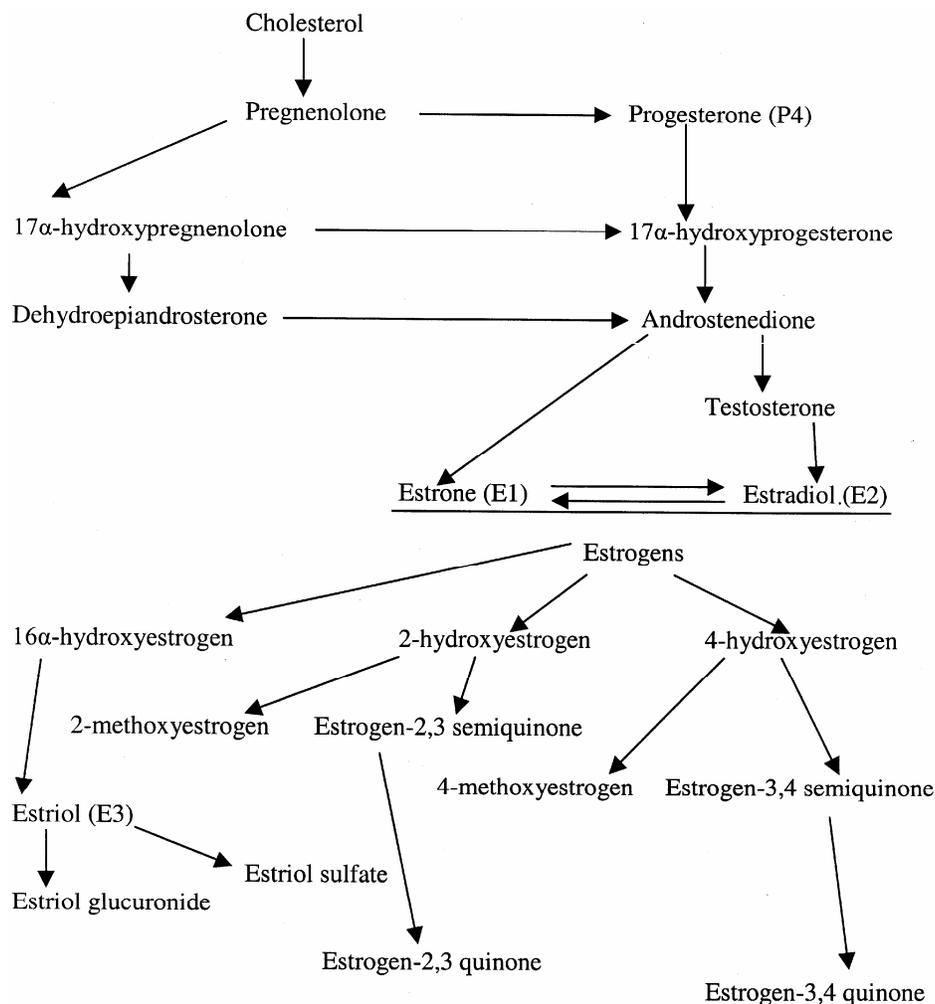

Fig. 1—Principal pathways of estrogen biosynthesis and metabolism

potential[19,20]. In addition, quinones and semiquinones undergo redox cycling, which results in the production of reactive oxygen species (ROS) that can cause oxidative damage to lipids, proteins and DNA[21]. However, several phase II enzymes such as catechol-*O*-methyltransferase (COMT), GST and superoxide dismutases (SOD) participate in catechol metabolism (Fig. 2). The inactivation of catechol estrogens by methylation is catalyzed by COMT. The observed lack of carcinogenic activity of the 2-hydroxyestrogens may be due to faster rate of methylation[20].

Xenobiotic metabolizing enzymes in breast tissue

Xenobiotic chemicals may exert their pathological effects through generation of ROS which has been related to the etiology of cancer, as they are known to be mitogenic to variety of cells, and therefore capable of tumor promotion[22]. ROS induces lipid peroxidation and generates toxic aldehydes like malondialdehyde (MDA) that may cause tumor promotion[23]. In addition, ROS has been found to modulate signaling events in the cells and plays a functional role in the pathogenesis of malignancy including breast cancer[24]. Human mammary tissues can be exposed to different agents which may cause oxidative stress and DNA damage. It was observed that lipid extracts from human breast

induced mutations and DNA damage[25]. Genotoxic activity was also found in a significant proportion of extracts from human breast milk[25]. Li *et al.* demonstrated that the major bulky DNA adduct detected in human breast tissues was related to polycyclic aromatic hydrocarbons (PAHs) exposure[26]. Also, tumour-adjacent breast tissues from cancer patients exhibited significantly higher levels of DNA adduct induced by MDA compared to non-cancer controls[27]. The levels of 8-hydroxy-2′-deoxyguanosine, an oxidized DNA base common in cells undergoing oxidative stress, in breast cancer tissues were significantly higher than those of their corresponding non-cancerous breast tissues[28]. Accumulating evidence suggests that the oxidative metabolites may contribute to estrogen-dependent carcinogenesis like breast cancer. Most of potential human mammary carcinogens require multiple enzyme-catalyzed steps for biotransformation to become DNA-reactive metabolites[29]. Xenobiotic metabolizing enzymes expressed in the breast tissue may have immense role in either activating or detoxifying both endogenous and exogenous compounds.

Several cytochrome P450 enzymes are detected in normal as well as cancerous breast tissues such as CYP1A1, CYP1B1, CYP2A6, CYP2B6, CYP2C9,
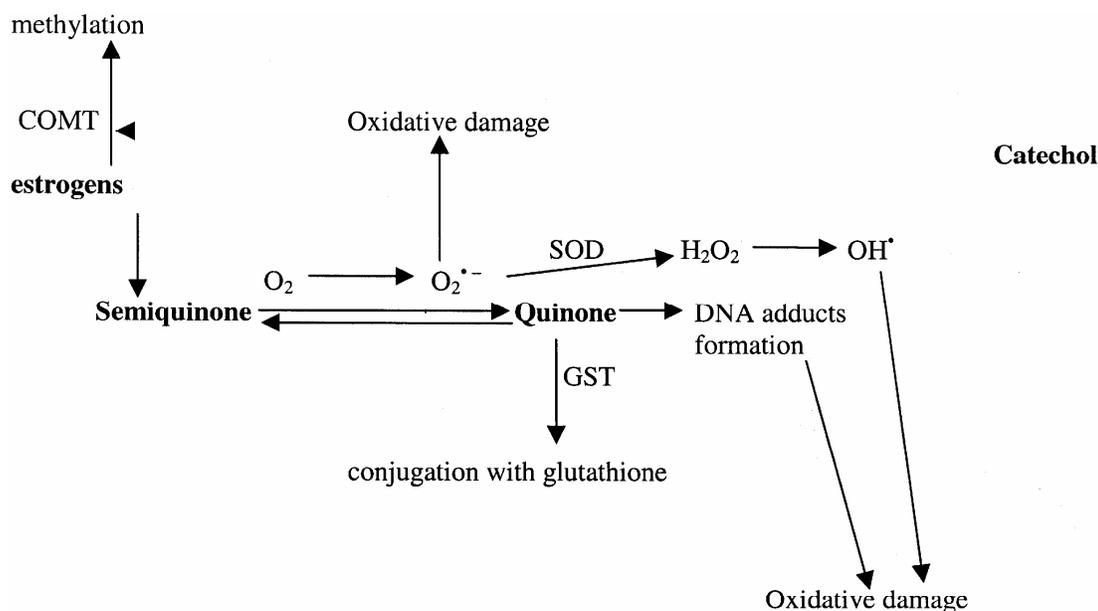
$O_2^{\bullet -}$: superoxide free radical
$OH^{\bullet}$: hydroxyl free radical

Fig. 2—Generation of reactive oxygen species (ROS) in estrogen metabolism

CYP2E1 and CYP3A4[30-32]. Although phase I enzymes such as CYP1A2, CYP2C6 and CYP3A4 are involved in hepatic and extrahepatic estrogen oxidation, CYP1A1 and CYP1B1 display their leading expression in breast tissue[21,29]. The 4-hydroxylation activity of CYP1B1 has received particular attention because of experimental evidence that 4-hydroxy catechol estrogens are more carcinogenic than the 2-hydroxy isomers[21]. On the other hand, several anti-oxidant and phase II enzymes are expressed in breast tissue. Studies observed higher activities of SOD in breast cancer[33,34]. Er *et al*. noticed 1.5-fold increase of MnSOD expression in breast cancer tissues compared to non-cancerous tissues[35]. Further, Thomas *et al*. recorded higher expression of both MnSOD and CuZnSOD in breast tumours[36]. Genetic polymorphism in the MnSOD gene (Ala/Ala genotype) was found to have increased risk of breast cancer among Chinese women with high levels of oxidative stress or low intake of anti-oxidant dietary factors[37]. Like SOD, catalase showed higher expression and activity in breast cancer tissues[34,36]. On the contrary, Tas *et al*. found significantly decreased activity of catalase in tumour tissues[33].

Human myeloperoxidase is expressed in neutrophils recruited to the lung; and the enzyme is also present in breast milk and blood[29]. Following immunological and/or chemical insults, neutrophils release myeloperoxidase and undergo a 'respiratory burst', which is characterized by a massive increase in oxygen consumption and a consequent NADPH-dependent production of superoxide and other free radicals[38]. Myeloperoxidase produces the potent bacteriotoxic oxidizing agent hypochlorous acid and ROS in physiological situations, which may also cause DNA damage[38,39] (Table 2). Probably, myeloperoxidase is particularly significant in breast cancer, as suggested by association between this enzyme activity and estrogen levels[40]. Because of the presence of myeloperoxidase in normal breast and tumour tissues of the breast, its association with estrogen levels, and its ability to generate ROS, myeloperoxidase may be important in the oxidative stress pathway in human breast cancer[41]. It is worthy to mention that methylation catalyzed by COMT is a necessary mechanism for preventing oxidative metabolites of catechol estrogens in order to protect DNA from oxidative damage. Expression of COMT is observed in the liver, kidney, breast and endometrium[42]. Further, the phase II enzyme GST is known to play a key role in the detoxification of both xenobiotic and endogenous compounds, and in the reduction of ROS and DNA adducts formation. Overall, GSTs form a group of multi-gene isoenzymes and on the basis of sequence similarity and immunological cross-reactivity[43-45], they have been divided into a number of subclasses (e.g., α, δ, ζ, θ, μ, π, σ and τ). GST π(pi) and μ(mu) are the major isoforms expressed in the breast tissues[32,46]. Among other phase II enzymes, sulfotransferase converts estrogens into the biologically inactive estrogen sulfates. On the other hand, steroid sulfatase hydrolyzes inactive estrogen sulfates to estrogens. Further, sulfotransferases catalyze the biotransformation of xenobiotic compounds. Usually, sulfonation by sulfotransferases leads to the inactivation of parent compounds; however, formation of more toxic metabolites can occur (Table 2). Several studies detected various isoforms of sulfotransferases in both normal and malignant breast tissues[47-49]. Another important phase II enzyme expressed in breast tissue is *N*-acetyltransferases. Evaluation of *N*-acetyltransferases (NAT) and sulfotransferases (SULT) enzyme expression in the breast has shown that major isoforms are NAT1, SULT1A1 and SULT1A3, all of which can activate xenobiotic compounds into DNA-reactive metabolites[38,50] (Table 2). Nevertheless, current evidence indicates a role of oxidative metabolites in the pathogenesis of breast cancer. Both in the xenobiotic and catechol estrogen metabolisms, there is a considerable inter-individual variability (polymorphism); and these person-to-person differences, which are attributed to polymorphisms in the genes encoding for the respective enzymes, may define subpopulations of women with risk for breast cancer[20].

Table 2—Adverse effects of selected anti-oxidant/phase II enzymes expressed in breast tissues

Enzymes	Common genotypes involved in xenobiotic metabolism (broadly classified)	Adverse effects/metabolic activation of xenobiotic compounds
Myeloperoxidase	*MPO* (*GG*, *GA*, *AA*)	heterocyclic amines, aromatic amines, PAHs
Glutathione-*S*-transferase	*GSTM1*, *GSTM3*, *GSTP1*, *GSTT1*	multi-drugs resistance of tumour cells
Sulfotransferase	*SULT1*, *SULT2*	PAHs, aromatic amines, heterocyclic amines
N-acetyltransferase	*NAT1*, *NAT2*	heterocyclic amines, aromatic amines

Effects of tobacco/cigarette smoking

Other than cancers of the directly affected organs such as respiratory system[51] and distant organs such as uterine cervix[52], smoking may increase the risk of breast cancer[53]. Various factors like duration and intensity of smoking[54], family history of breast cancer[55], cigarette smoking during first pregnancy[56] etc. are found to influence the smoking induced risk of breast cancer. Also, a direct relationship was observed between cigarette smoking and metastasis in breast cancer[57]. However, the association between tobacco smoking and breast cancer risk has remained controversial [58-60].

Many lipophilic carcinogens of tobacco smoke[20] e.g., PAHs like benzo[a]pyrene, heterocyclic amines such as 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) (Fig. 3) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), aromatic amines such as 4-aminobiphenyl, and N-nitrosamines[61] can be stored in breast adipose tissue[59]. Some PAHs such as 7,12-dimethylbenz[a]anthracene (DMBA) and dibenzo[a,l]pyrene (DB[a,l]P) are potent mammary tumourigens in the rat and are metabolically activated through formation of diol-epoxides[62]. Also, cigarette smoke is a rich source of ROS which can cause oxidative damage[63]. Nitrosamines and other carcinogenic compounds are present in higher concentration in passive smoke due to incomplete combustion that occurs when the tobacco burns at lower temperature and because of the unfiltered side-stream/passive smoke[64]. Howsoever, controversies exist on the risk of breast cancer by passive smoking also [65-68].

The polymorphisms in genes encoding detoxifying enzymes such as CYP1A1, CYP1B1, CYP1A2, COMT, GST, epoxide hydrolase, SULT, peroxidases and NAT have been reported to modify the tobacco smoke carcinogens in breast tissue[29,64]. In this regard, NAT is the most extensively studied enzyme; NAT enzymes are encoded by the *NAT1* and *NAT2* genes. Whether acetylation status (fast or slow acetylator according to *NAT2* genotypes) influences breast cancer risk in both active and passive smoking is a controversial issue. However, majority of the studies found that smoking was associated with an increased risk of breast cancer in *NAT2* slow acetylators[69-71].

Environmental endocrine disruptors

Many studies have implicated several chemicals in the pathogenesis of breast cancer, including therapeutic agents such as antibiotics and anti-hypertensive drugs[72-76]. However, this review article
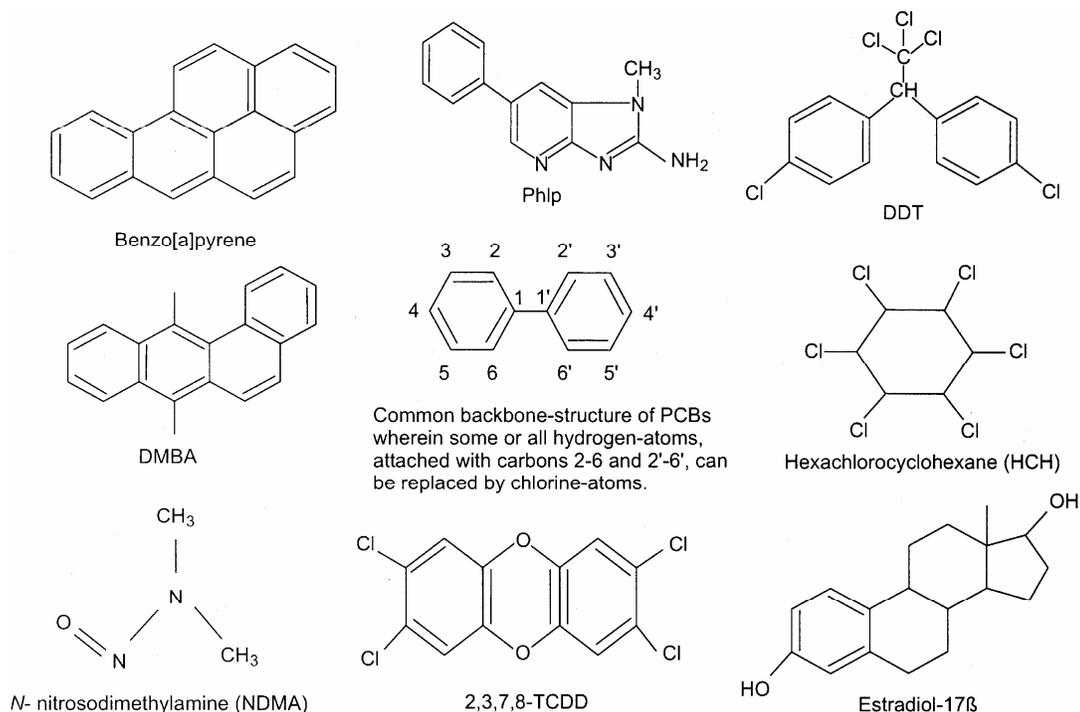

Fig. 3—Selected environmental carcinogens along with estrogen (usually, these chemicals have a structural similarity with estrogen).

has tried to concentrate on a small number of chemical contaminants which exist in the environment. The concept of 'endocrine disruptors' is an emerging subject that has gained popularity among both public and scientific community following publication of the book '*Our Stolen Future*' by Theo Colborn and colleagues[77] in 1996. Endocrine disruptors are xenobiotic chemicals that adversely interfere with the natural functions of hormones (Table 3). Estrogenic endocrine disruptors or xenoestrogens are widely distributed in the environment[78,79]. Numerous chemicals such as pesticides, polychlorinated biphenyl congeners (both have been discussed in the next section), food-related mycotoxin zearalenone and its derivatives, ultraviolet screen 3-(4-methylbenzylidene)-camphor (4-MBC) and even some metals like cadmium can influence hormonal responses by binding to estrogen receptor (ER). This phenomenon is the most commonly studied mechanism by which environmental chemicals exert their effects on breast. The xenoestrogens interact with the binding pocket of the ER because they have chemical similarities to estrogen (usually a phenolic A-ring). However, reduced activity of xenoestrogens probably results from lack of fit of the remainder of the molecule within the binding pocket[79]. As discussed earlier, several xenobiotic chemicals may interact with the enzyme systems that metabolize estrogens; and by this process, they can modulate the endogenous steroid metabolism.

A number of chemicals such as organotin compound triphenyltin and fungicides fenarimol, procymidone, vinclozolin etc. inhibit steroid hormone synthesis. Alternatively, synthetic compound like diethylstilbestrol (DES) interfere the bio-availability and overall functions of estrogen by interacting with steroid hormone binding proteins in the blood such as sex hormone-binding globulin (SHBG) and albumin. Chemicals like retinoids, certain pyrethroid insecticides (e.g., sumithrin), pentachlorophenol and β-hexachlorocyclohexane alter steroid signaling pathways. Some compounds are able to disrupt estrogenic responses through several mechanisms. For instance, dioxins alter steroid hormone metabolism as well as there is a cross-talk between dioxin- and estrogen-mediated signaling pathways (vide 'Aryl hydrocarbon receptor and breast cancer' section). There are other mechanisms by which xenobiotic chemicals can influence the physiological functions of

estrogen such as adverse effects on release and excretion of hormones, disruption of regulatory feedback relationships between two endocrine organs, and modulation of non-genomic pathways.

Several investigators believe that endocrine disruptors may play a role in breast cancer incidence in the developed countries[79-83]. Perhaps this view is also true for the countries that are in the process of westernization. Recently, Kortenkamp has hypothesized the possibility of combination effects by a large number of xenobiotic chemicals, all may present at low levels in women's body, in the pathogenesis of breast cancer[83]. Howsoever, exploring the mechanisms of pathological effects by different endocrine disruptors is a challenging field. Identifying

Table 3— Man-made chemicals which can act as endocrine disruptors (related with estrogens)

Compound	Principal use/Source	Hormonal character
Atrazine	herbicide	estrogenic
Bisphenol A	manufacture of plastics	estrogenic
Butylhydroxyanisole	manufacture of plastics	estrogenic
Cyclotetrasiloxanes	rubber, plastics, and shampoo	hormonal modulator
DDT	insecticide	estrogenic
Dieldrin	pesticide	estrogenic
DES	synthetic estrogen/drug	estrogenic
Endosulphan	pesticide	estrogenic
Ethynylestradiol	synthetic estrogen/drug	estrogenic
Fenarimol	fungicide	anti-steroid
Hexachlorophene	disinfectant	anti-estrogenic
Kepone	insecticide	estrogenic
4-MBC	organic sun screen	estrogenic
Methoxychlor	insecticide	estrogenic
Menadione	synthetic vitamin K (K3)	anti-estrogenic
Nonylphenol	manufacture of rubber and plastics	estrogenic
o-phenyl phenol	fungicide, dye, rubber and disinfectant	estrogenic
Phthalates	plastics, fixatives for perfume	estrogenic
Pentachlorophenol	pesticide and wood preservative	anti-estrogenic
PCBs	plasticizers, dyes and coolants	estrogenic
PAHs	burning of organic substances	anti-/estrogenic
Triphenyltin	algicides and molluscicides	steroid inhibitor
Toxaphene	insecticide	estrogenic
Vinclozolin	fungicide	anti-steroid

the pathways of action is of great concern not only for preventive strategy but such discoveries may elucidate new signaling pathways leading to the development of selective ER modulators[84]. Already, this concept has become the working hypothesis for many researchers. It has been mentioned above that the aryl hydrocarbon receptor (AhR) or dioxin receptor has an involvement with the ER-mediated response pathways. Apart from dioxins, the AhR can be activated by a wide range of structurally diverse chemicals including different dietary substances. Therefore, modulation of the AhR activity in a favorable way may be possible by appropriate ligand(s). In fact, there is an effort to identify suitable ligands for the AhR in order to develop

chemotherapeutic agents against breast cancer[85]. In this connection, a well-classified list of ligands has been provided (Table 4).

Pesticide residues and breast cancer

Pesticides have become a part of the environment as contaminants due to their widespread use in agriculture and disease control programmes (Table 5). In the previous section, their endocrine disruption activity has been mentioned. It has been thought that some pesticides and related chemicals may act as carcinogens[86,87]. These xenobiotic compounds have been shown to enhance oxidative stress and lipid peroxidation in various tissues[88-90], and adversely affect the lymphocyte function[91]. It may be worthy to

Table 4—Different chemicals that can act as a ligand and modulate the AhR

Compounds	Source
I. Environmental pollutants/toxicants	
Halogenated aromatic hydrocarbons (HAHs)/dioxins (eg, TCDD)	Machinery process involving chlorine and phenolic substrates
Polycyclic aromatic hydrocarbons (PAHs) benzo[a]pyrene, 3-MC)	Incomplete pyrolysis of organic substances
Polychlorinated biphenyls (PCBs) (e.g., congeners 77, 126, 156)	Electrical substances
Heterocyclic amines (Ref.: 180, 182)	Cooking muscular tissues at high temperature
II. Endogenous compounds	
7-Ketocholesterol	Oxidized cholesterol/oxysterol
Lipoxin A4	Arachidonic acid metabolite
Bilirubin and biliverdin	Heme breakdown products
Tryptophan-related compounds:	
Tryptamine and indole acetic acid	Tryptophan metabolites
6-Formylindolo[3,2-*b*]carbazole (FICZ)	Tryptophan photoproduct
Indolo[3,2-*b*]carbazole and 3,3′-diindolylmethane	Gastric indole-3-carbinol
Indigo and indirubin	Human urinary products
III. Natural dietary compounds **Flavonoids:**	
Flavones (e.g., apigenin, luteolin)	Celery, sweet red pepper
Flavonols (e.g., kaempferol, quercetin)	Onions, apples, broccoli, grapes
Flavanones (e.g., hesperetin, naringenin)	Oranges, lemons, prunes
Flavanols or catechins (e.g., EGCG)	Green tea, black tea, plums
Isoflavones (e.g., genistein, equol)	Soya beans, chickpeas, legumes
Carotinoids:	
(canthaxanthin, astaxanthin, lutein, β-apo-8′-carotenal)	Carrots, tomatoes, apricots, pineapple, strawberry
Phenolcarboxylic acid & related compounds:	
Resveratrol	Grapes, berries, peanuts
Curcumin (turmeric)	Rhizome of *Curcuma longa*
Other compounds: (e.g., piperine, rosmarinic acid)	
IV. Synthetic compounds	
Synthetic flavones: (e.g., β-naphthoflavone)	
Drugs: (e.g., omeprazole, mevinolin, thiabendazole)	
Pesticides: (e.g., carbaryl, cypermethrin)	

Table 5—Selected pesticides categorized by chemical class

Insecticides

Carbamate:	carbaryl, carbosulfan, pirimicarb, aldicarb, methomyl, oxamyl, methiocarb
Organochlorine:	DDT, HCH, lindane, methoxychlor, pentachlorophenol, aldrin, chlordane, dieldrin, endosulfan, endrin, heptachlor:
Organophosphorous:	dichlorvos, monocrotophos, malathion, dimethoate, omethoate, phoxim, chlorpyrifos, diazinon, pirimiphos-methyl, quinalphos, fenitrothion, parathion, parathion-methyl, profenofos, trichlorfon
Pyrethroid:	bioallethrin, deltamethrin, fenpropathrin, fenvalerate, permethrin, sumithrin, cypermethrin

Herbicides

Amide:	isoxaben, pentanochlor, alachlor, metolachlor, chlorthiamid
Quaternary ammonium (Dipyridyl):	paraquat, diquat
Phenoxy:	2,4-dichlorophenoxy acetic acid (2,4-D), 2,4,5-trichlorophenoxy acetic acid (2,4,5-T), 2,4,5-trichlorophenoxy propionic acid (2,4,5-TP)
Triazine:	atrazine, simazine, cyanazine, atraton
Unclassified group:	oxadiazon, pentachlorophenol

mention that the immune surveillance mechanism mostly by T-cell mediated function continuously eliminates the cells transformed into malignancy; and many pesticides are immunotoxic and found to suppress the cell-mediated immunity. Burow *et al.*[92] demostrated that pesticides such as DDT and alachlor can behave like endogenous estrogen and function to suppress apoptosis in ER-positive MCF-7 human breast cancer cells. Therefore, it is reasonable to consider a relationship between pesticide exposure and breast cancer risk[93,94]. The data of different investigators are inconsistent. Several studies did not support this hypothesis[95-98]. However, many investigators observed a positive association[90,99-109].

Organochlorine compounds are a diverse group of synthetic chemicals such as dichlorodiphenyltrichloroethane (DDT), dieldrin, hexachlorocyclohexane isomers (HCH), toxaphene, polychlorinated biphenyls (PCBs) and dioxin (Fig 3). DDT was the first widely used and also the most widely studied pesticide. Although, use of DDT has been banned in the developed countries since 1970s, this pesticide use is continuing in some developing countries including South Asian region[110,111]. The most prevalent breakdown product of DDT is dichlorodiphenyldichloroethylene (DDE) that persists in the environment, concentrates up the food chain, is stored in fatty tissues of animals, fish, and human, is widely detected in breast milk and cow's milk, and has been detected in household dust and air[110]. Estrogenic activities of some DDT metabolites are more than DDT itself, with reasonably long biological half-life. PCBs represent a large and diverse class of

organochlorine chemicals that include approximately 209 individual chlorinated compounds known as congeners[112,113]. PCBs have been used as coolants and lubricants in electric appliances such as transformers and capacitors. The manufacture of PCBs was stopped in the United States in 1977 because of evidence that they build up in the environment and can cause health hazards. PCBs enter the air, water and soil during their manufacture, use and disposal; humans consume PCBs when they eat contaminated foods[113]. The common features of all these above-mentioned compounds are their persistence in the environment, their bioaccumulation in adipose tissue and in food chains due to lipophilic character, and their resistance to metabolism. It has been hypothesized that the lipid-soluble carcinogens released from the adipose tissue in the human breast may influence the ductal epithelial cells, from which breast tumours commonly arise[25]. Therefore, deposition of these chemicals in the adipose tissue of the breast has been linked to its neoplastic transformation. Overall, the investigation on the association between pesticide exposure and breast cancer risk faces various issues, which may explain the inconsistency in the results amongst different studies such as ethnic groups or genetic predisposition of population, lifestyle factors, and other environmental aspects[107].

Role of food mutagens

It has been thought that diet has an influence on cancer development, and a part of the risk may be associated with the consumption of mutagenic

substances along with the foods. Several compounds, either present as dietary components or contaminants or formed during food processing, can play a role in cancer risk. For instance, some dairy products like whole milk and different types of cheese contain high levels of saturated fat, which may increase risk. Moreover, milk products may contain growth factors such as insulin-like growth factor-I, which have been shown to promote breast cancer cell growth, and pesticide residues[114]. Recently, Coyle *et al.*[115] observed in their study that styrene was the most important environmental toxicant positively associated with invasive breast cancer incidence. Styrene is used as a building block for polymers in plastics, resins, coatings and paints; however, it can be found in a variety of vegetables, beverages and meats. Further, food related mycotoxin zearalenone and its derivatives such as α-zearalenol, β-zearalenol, α-zearalanol and β-zearalanol can bind to ER and exert estrogenic action[116]. Zearalenone is a non-steroidal compound produced by several *Fusarium* fungi species which contaminate dairy products and cereals such as barley, corn, maize, rice, wheat, etc. It has been hypothesized that zearalenone may be a potential promoter of breast tumourigenesis[117]. After consumption, food mutagens undergo metabolic activation or detoxification by different endogenous enzymes. Most mutagens begin their adverse effects at the DNA level by forming DNA adducts with carcinogenic metabolites[118]. Nevertheless, there are some non-genotoxic carcinogens like chloropropanols. In experimental animals, 3-monochloropropanediol (3-MCPD) and 1,3-dichloro-2-propanol (DCP) have been shown to produce neoplastic lesions in various sites including mammary gland[119]. These compounds are produced in roasted or toasted cereal products, bread and biscuits, cooked meats and cheese, and some soy sauces[119,120]. Usually, chloropropanols are present in savoury foods, which contain extracts of protein-rich vegetables, prepared at high temperature. Similarly, high levels of acrylamide have been detected mainly in carbohydrate-based foods that are cooked at high temperature deep-frying and baking such as in potato chips, French fries and crisps. Acrylamide in food is largely derived from heat-induced reactions between the amino group of the free amino acid asparagine and the carbonyl group of reducing sugars (linked to the Maillard reaction)[121,122]. Acrylamide is a water-soluble

compound and readily absorbed in the body. This compound is biotransformed *in vivo* to its chemically reactive epoxide, glycidamide, which form DNA adducts[123]. It has been shown that orally administered acrylamide increased the incidence of mammary tumours in experimental animals[124].

The *N*-nitroso compounds are a large group of chemicals that have been linked with the pathogenesis of cancer. Broadly, *N*-nitroso compounds are classified into two groups: *N*-nitrosamines (Table 6) and nitrosamides (e.g., *N*-nitrosureas, *N*-nitrosocarbamates, *N*-nitrosoguanidines, etc.). Humans are exposed to *N*-nitrosamines in diet from a variety of cured meats and fish products; also, these compounds can be formed *in vivo* during simultaneous ingestion of nitrite or nitrogen oxides and a nitrosable substrate such as a secondary amine[118,125-127]. Usually, carcinogenic properties are present in volatile *N*-nitrosamines. However, non-volatile *N*-nitrosamines can be converted to volatile compounds. In diet, *N*-nitrosodimethylamine (NDMA) (Fig. 3) has been detected most frequently, among volatile *N*-nitrosamines[128-130]. NDMA undergoes enzymatic hydroxylation mainly by CYP2E1 and subsequent hydrolysis to an aldehyde and a monoalkylnitrosamine, which finally forms carbo-cation that is reactive to DNA bases[121]. Experimental animal models support the carcinogenic properties of *N*-nitrosamines, and cancer of various sites including mammary gland has been reported[131]. It has been mentioned earlier that tobacco smoke contains different *N*-nitrosamines. Tobacco-specific nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN), are by far the most prevalent strong carcinogens in unburned tobacco[132]. Interestingly, some pesticides like atrazine can be converted into genotoxic *N*-nitrosamines (*N*-nitrosoatrazine) in the environment or the digestive system[133].

Polycyclic aromatic hydrocarbons (PAHs) are formed during the incomplete combustion of coal, oil, gas, garbage, and other organic substances such as tobacco and different food items. Grilling or broiling of meat, fish or other foods over a direct flame leads to fat dripping on the hot fire and yielding gleams containing of PAHs that deposit on the surface of the food materials. Moreover, formation of PAHs is directly related with the intensity of the heat[121]. PAHs are ubiquitous environmental contaminants; the presence of PAHs has been demonstrated in a wide

Table 6—Dietary mutagens, which may have relation with the pathogenesis of breast cancer, and their metabolizing enzymes

Mutagenic chemicals	Principal metabolizing enzymes
Acrylamide and glycidamide	CYP2E1, epoxide hydrolase, GST
Heterocyclic aromatic amines	CYP1A2, NAT, SULT, GST
Polar	
Imidazoquinoline: IQ, MeIQ	
Imidazoquinoxaline: MeIQx	
Imidazopyridine: PhIP	
Non-polar	
Pyridoimidazole/Pyridoindole: Trp-P-1, Trp-P-2,	
Glu-P-1, Glu-P-2, AαC	
MeAαC	
***N*-nitrosamines**	CYP2E1, CYP2A6
Volatile	
N-nitrosodimethylamine	
N-nitrosodiethylamine	
N-nitrosopyrrolidine	
N-nitrosopiperidine	
N-nitrosomethyl-benzylamine	
Non-volatile	
N-nitrosoproline	
N-nitrosothiazolidine-4-carboxylic acid	
Polycyclic aromatic hydrocarbons (PAHs)	CYP1A1, CYP1B1, epoxide hydroxylase, GST, glucuronyl transferases
Benzo[a]pyrene	Benzo[b]fluoranthene
Dibenz[a,h]anthracene	
Benzo[b]fluoranthene	
Indeno[1,2,3-cd]pyrene	

variety of plants and aquatic organisms[134,135]. Leafy vegetables can be a significant source of PAHs in the human diet; the level of contamination is governed by where the vegetables are grown, those situated close to roads being particularly likely to be contaminated with PAHs[136]. Although few epidemiological studies have been conducted for chemical exposure, occupational studies show association between breast cancer and exposure to PAHs[137]. Nevertheless, benzo[a]pyrene is the best-characterized PAH compound available from the diet[118] (Table 6). Metabolic activation of PAHs results in DNA binding products via diol-epoxide formation[138], In general, PAHs occur in lower amount in cigarette smoke; human exposure is predominantly from dietary sources.

Observation at the later part of the 19th century that occupational exposure in the dye industry led to the development of urinary bladder cancer was a landmark discovery in order to understand the carcinogenic role of aromatic amines (arylamines). People can be exposed to different types of aromatic amines, which are present in the environment, diet and tobacco. Overall, aromatic amines can be classified into monocyclic aromatic amines (e.g., aniline, *o*-toluidine or 2-methylaniline and 4-chloro-*o*-toluidine), polycyclic aromatic amines (β-naphthylamine, 4-aminobiphenyl and benzidine) and heterocyclic aromatic amines (Table 6). Most heterocyclic amines, many polycyclic aromatic amines, and some monocyclic aromatic amines are mutagenic[139]. Cooking meat and fish at high temperature produces heterocyclic amines. Generally, heterocyclic amines are formed from creatine or creatinine, amino acids and carbohydrates, e.g., phenylalanine, creatinine and glucose are probable precursors of PhIP[140]. It has been observed that higher consumption of meat probably associated with an increased risk of breast cancer[141,142]. A case-control study in Uruguay showed a correlation between exposure to meat heterocyclic amines and breast cancer risk[143]. Studies of the amount of heterocyclic amines produced in foods of different cooking practices have revealed that PhIP and 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx) are the most abundant heterocyclic amines[144]. The International Agency for Research on Cancer (IARC) has classified IQ as a possible human carcinogen (Group 2A) and other heterocyclic amines such as 2-amino-2,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ), 2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQ-x), PhIP, 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC), 2-amino-3-methyl-9*H*-pyrido[2,3-*b*]indole (MeAαC), 3-amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-1), 3-amino-1-methyl-5*H*-pyrido[4,3-*b*]indole (Trp-P-2), 2-amino-6-methyl-dipyrido[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-1) and 2-amino-dipyrido[1,2-*a*:3′,2′-*d*]imidazole (Glu-P-2) as probable human carcinogens (Group 2B)[145]. The proposed bioactivation pathway of heterocyclic amines consists of *N*-hydroxylation by CYP1A2, and subsequent acetylation; the nitrenium ion (derived from the exocyclic amino group of the imidazo-moiety) is the likely ultimate carcinogen binding to the DNA bases[118,121].

Aryl hydrocarbon receptor and breast cancer

Aryl hydrocarbons such as dioxins, PCBs and PAHs bind to the cellular aryl hydrocarbon receptor

(AhR); and the activation of intracellular signaling subsequent to the AhR binding is highly correlated with the toxicity and carcinogenicity of these chemicals[146]. Dioxins belong to a group of halogenated aromatic hydrocarbons (HAHs), which have a similar chemical structure and biological effects. This group includes 7 polychlorinated dibenzo dioxins (PCDDs), 10 polychlorinated dibenzo furans (PCDFs) and 12 PCBs[147]. Dioxins are derived from combustion process (e.g., incineration and burning of fuels), during production and utilization of chlorinated compounds (e.g., PCBs) and bleaching of paper-pulp. Humans are exposed to dioxins mainly through the consumption of contaminated foods. Among these compounds, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) (Fig. 3) is a persistent lipophilic environmental contaminant (half-life ~7years) and considered as the prototype chemical. Much attention has been focused on TCDD for several reasons. TCDD is the most toxic congener and an animal non-genotoxic carcinogen. Further, TCDD was used in Vietnam War (with Agent Orange) between 1962 and 1971; and there was a major industrial accident in Seveso of Italy in 1976, which resulted in the highest known population exposure to TCDD. It has been observed that increased serum TCDD levels were significantly related with breast cancer incidence among females in the Seveso Women's Health Study (SWHS) cohort[148]. The median serum TCDD level for

women with breast cancer (median = 71.8 ppt, interquartile range 47.3–200.0) was greater than for women without breast cancer (median = 55.1 ppt, interquartile range 27.8–153.0). Cox proportional hazards modeling showed a 2-fold increase of risk for a 10-fold increase in serum TCDD. Moreover, approximately 20 years after the Seveso accident, the expression of AhR gene was found to be decreased in the exposed subjects and negatively correlated with blood TCDD levels[149,150].

Earlier reports also showed an increased breast cancer incidence[151] and mortality[152,153] among female workers occupationally exposed to TCDD. Moreover, high levels of dioxins including TCDD were detected in the environment of Chapaevsk, Russia, due to industrial pollution. Also, it has been reported that Chapaevsk women have a higher risk for breast cancer[154]. In a study conducted by Brown *et al.*[155], prenatal TCDD treatment resulted in an increased number of chemically induced mammary adenocarcinomas in experimental animals. Further, evidence suggests that exposure to dioxin-like PCBs increases risk for breast cancer[156]. The studies which showed a positive association between breast cancer risk and pollutants that are considered as ligands for the AhR have been summarized in the Table 7[99,101,102,106,148,151-154,156-165].

It has been mentioned earlier that TCDD exposure causes a persistent alteration in the AhR expression

Table 7—Salient findings of the epidemiological studies which showed a positive association between breast cancer risk and pollutants that are considered as ligands for the AhR (reports in chronological order).

Investigators	Observations
Manz *et al.*[152]	Increased breast cancer mortality among female workers occupationally exposed to TCDD.
Kogevinas *et al.*[153]	Increased risk for cancer in workers exposed to dioxins.
Flesch-Janys *et al.*[151]	Increased incidence of breast cancer in female workers exposed to dioxins.
Revich *et al.*[154]	Higher risk of breast cancer in a Russian town contaminated with TCDD from industrial source.
Warner *et al.*[148]	Increased breast cancer incidence among women with higher serum TCDD levels in the SWHS cohort.
Wassermann *et al.*[157]	Higher PCBs in adipose tissue of breast cancer patients.
Falck Jr *et al.*[158]	,,
Liljegren *et al.*[159]	Increased levels of PCB #77, 126 and 169 in adipose tissue of postmenopausal breast cancer.
Guttes *et al.*[160]	Higher concentrations of PCB #118, 153 and 180 in breast cancer tissue.
Aronson *et al.*[99]	Higher levels of PCBs in adipose tissue of breast cancer.
Lucena *et al.*[161]	Higher adipose tissue levels of PCB #28 and 52 in breast cancer cases.
Woolcott *et al.*[101]	Positive association between breast adipose tissue PCBs and poor prognosis.
Demers *et al.*[156]	Higher plasma concentrations of PCB #99, 118 and 156 in breast cancer.
Hoyer *et al.*[102]	Higher serum levels of PCBs among cases with mutant p53.
Muscat *et al.*[106]	Association between adipose tissue PCB concentrations and tumor recurrence.
Zhang *et al.*[162]	Modification of the association between PCB exposure and breast cancer risk by CYP1A1 m2 variant genotype.
Li *et al.*[163]	,,
Petralia *et al.*[164]	Association between PAH exposure and ER-positive breast cancer.
Bonner *et al.*[165]	Association between PAH exposure in early life and postmenopausal breast cancer risk.

among affected subjects in Seveso. Human studies examining the AhR are few, probably due to the fact that investigators are more interested in functional significance of AhR and the suitability of CYP1A1 or CYP1B1 as a biomarker in epidemiological studies related with the AhR[147,166]. However, remarkably little genetic variation has been detected in the human AhR gene[167]. In a study on breast cancer tissue, Dialyna *et al.* observed that AhR gene was frequently deregulated in an independent manner[168]. On the other hand, study on human breast cancer cell lines revealed that AhR expression levels were highly dependent on cell types[169]. Further, over-expression of the AhR was noticed in rat mammary tumor tissue[170].

Toxic chemicals such as TCDD, benzo[a]pyrene and PCBs like congener 126 can activate AhR, which subsequently induce CYP1A1 and CYP1B1 expression[171]. Interestingly, estradiol is metabolized by CYP1A1 and CYP1B1, which also activate benzo[a]pyrene to reactive DNA-binding intermediates[172,173]. There is evidence of cross-talk between estrogen receptor-α (ERα) and AhR-mediated signaling in breast and endometrial cells[174]. On the other hand, oxidative stress caused by the induction of cytochrome P450 enzymes is one of the toxic effects of dioxin. Further, transforming growth factor-α (TGFα) plays a pivotal role in the dioxin-induced activation of the epidermal growth factor receptor (EGFR) and the extracellular signal-related kinase pathway, which acts as a signal to suppress apoptosis induced by cellular stress[175]. In addition, Angus *et al.*[176] observed in ER-positive breast cancer cells that TCDD induced the expression of c-erbB-2 and c-erbB-3, the other members of EGFR family. Apart from the above-mentioned mechanisms, dioxins and related PCBs have immunosuppressive effects that may play an important role in carcinogenic process. TCDD exerts adverse effects by activating AhR in both B- and T-cells[177,178]. Overall, TCDD and structurally similar HAHs cause a broad range of immunological effects in experimental animals including decreased host resistance to infectious disease and suppressed humoral and cell-mediated immune response[147]. Similarly, many PAHs (e.g., benzo[a]pyrene and DMBA) are potent immunotoxic agents; and the AhR is known to mediate many effects of PAHs, including immunotoxic effects that could indirectly contribute to the carcinogenic properties of PAHs[179].

The AhR is a cytoplasmic basic helix-loop-helix/Per-Arnt-Sim homology (bHLH/PAS) protein, which in the unbound state (95-110 kDal) forms a complex with two chaperone heatshock proteins (Hsp90), a small protein (p23), and an immunophilin-like protein (XAP2)[175,180,181]. The transcriptional regulators Per (Period) and Sim (Single minded) were first characterized in *Drosophila*. Upon binding with ligand such as TCDD, benzo[a]pyrene or 3-methylcholanthrene (3-MC), the complex dissociates and the AhR translocates into the nucleus, where it dimerizes with another basic helix-loop-helix protein called AhR nuclear translocator (ARNT) (Fig 4)[181,182]. Finally, AhR acts as a nuclear transcription factor by binding to the dioxin/xenobiotic responsive element (DRE or XRE), resulting in the activation of several genes involved in xenobiotic metabolism such as CYP1A1, CYP1A2 and CYP1B1[183]. The induction of CYP1A1 activities has been referred to as aryl hydrocarbon hydroxylase (AHH)[1,184]. However, it has been suggested that the AhR acts in connection with some other pathways like TGF-β and ER-mediated signal transduction pathways[185,186]. Recently, Matthews *et al.*[187] have demonstrated a mechanism where ERα acts as a co-regulator of AhR-mediated transcriptional activation. Furthermore, compounds such as PAHs, which do not bind ER, may modulate estrogen activity by means of the AhR[188]. On the other hand, Mimura *et al.*[189] isolated a protein of bHLH/PAS family, the aryl hydrocarbon receptor repressor (AhRR) that acts as a negative regulator of the AhR function by competing with AhR for ARNT and by forming AhRR-ARNT complex[190]. Apart from
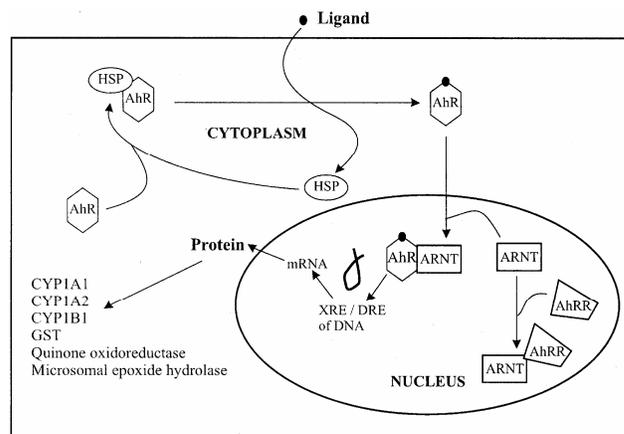

Fig. 4—Sequence of events after binding of the ligand to the AhR (The AhR dissociates from chaperone (Hsp90) and the AhR-ligand translocates into the nucleus to dimerize with ARNT, which acts as a nuclear transcription factor for several genes. The AhRR functions as a negative regulator by forming AhRR-ARNT complex)

environmental contaminants such as dioxins and PAHs, the AhR can bind with a variety of structurally diverse chemicals[191] (Table 4). Several investigators have observed that different dietary components, e.g., flavonoids, carotinoids, resveratrol, etc., bind to the AhR; and many of them exert antagonistic activity[182,191,192]. Some dietary components like indolo[3,2-*b*]carbazole closely resembles dioxin in structure. In acidic environment of the stomach, indolo[3,2-*b*]carbazole and 3,3′-diindolylmethane are produced from indole-3-carbinol derived from glucosinolates of consumed cruciferous vegetables such as broccoli, cabbage and cauliflower. Interestingly, Chen *et al.*[193] commented that resveratrol can act as a potential chemopreventive against dioxin-induced human mammary carcinogenesis by blocking the reactive metabolite formation of the catechol estrogens and scavenging the ROS generated during their redox cycling. Overall, a dietary modification with the introduction of increased quantities of soybean-products, cruciferous vegetables, fruits, curcumin, tea and low fat could be beneficial in reducing the risk of developing cancer and possibly the adverse effects of different environmental contaminats[194-196].

It is known that TCDD produces an AhR-dependent oxidative stress in mitochondria[197]. This phenomenon is associated with concomitant loss of mitochondrial membrane potential, a reduction in mitochondrial glutathione levels and mitochondrial DNA (mtDNA) damage[198,199]. Further, Banzet *et al.* observed that mitochondria could be a target for ROS-mediated effects of tobacco smoke exposure[200]. Alternatively, mitochondrial dysfunction may contribute to increased ROS production and play a role in tobacco carcinogenicity[201]. Lipophilic carcinogens such as PAHs accumulate in mitochondria and can cause mtDNA damage[202]. The incidence of mtDNA damage is 10- to 15-fold greater compared to nuclear DNA, since mtDNA has no protective histones. Nevertheless, it is possible to partially counteract the deleterious effects of benzo[a]pyrene, a prototypical PAH, on mitochondrion-related apoptotic process by blocking the AhR[203]. Mechanisms of toxicity of several pesticides such as 2,4-dichlorophenoxyacetic acid (2,4-D) and paraquat are associated with a disruption of mitochondrial membrane potential[204,205]. Growing evidence suggests that cancer cells exhibit increased intrinsic ROS stress due in part to mitochondrial malfunction that also alters cellular architecture, signaling, metabolism, cell growth and differentiation, and apoptotic response to anticancer agents[206,207].

Conclusions

The recent increasing trend in the incidence of breast cancer in urban population has drawn attention of all sections of the society. Attempts have been made to find out the causes of this increasing trend by different research initiatives. Many lifestyle factors have been incriminated in this regard. With the discovery and increasing use of pesticides, westernized food habits and due to other industrialized products, the levels of environmental contaminants are increasing day by day. As discussed in the review, these xenobiotics by various mechanisms are capable of contributing to pathogenesis of breast cancer. For many such chemicals, the potential of carcinogenicity and the mechanisms of action have not been evaluated till date. For some environmental contaminants, it is partially understood. Laboratory animal experimentation and reports of higher levels of the concerned environmental contaminants in breast cancer cases indicate that these environmental chemicals may be a confounding factor in the increasing prevalence of breast cancer. Knudson's double hit hypothesis has shown how environmental insult/hit can lead to cancer in genetically susceptible subjects. There is no doubt that with increasing levels of environmental chemical contaminants, the chances of getting exposed to such environmental insults are more. Frequent exposure and higher doses of such insults can possibly induce cancer in subjects who are not even genetically susceptible. But how much is the real impact of these chemical contaminants in breast cancer pathogenesis is yet to be determined. This is the time to think about the inclusion of new parameters like AhR activation and other potential pathways of endocrine disruptors, apart from E-screen assay, in evaluation of toxicity profile of pesticides and other xenobiotics. Obviously, there is an urgent need for systematic study to evaluate the impact. Such studies can explore possible reasons for the difference in prevalence of breast cancer in rural and urban areas and in different ethnic groups. Also, this process may lead to discovery of complex interplay of xenobiotics in induction of cancer and new dimensions in gene-environment interactions. Only a clear understanding could lead to an efficient strategy of breast cancer prevention.

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