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Cancer pathogenesis caused by xenoestrogens of environment and food contaminants: A Review

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ABSTRACT

The environmental and food contaminants, including therapeutic agents (e.g, antibiotics, antihypertensive drugs, etc.) and oestrogenic endocrine disruptors (xenoestrogens or xenobiotic chemicals), which mediate the oestrogens may lead to the development of cancer. Oestrogens and their metabolites are involved in the cancer pathogenesis of breast, uterus, ovary, pituitary gland, testicle, liver, kidney and bone marrow. Xenoestrogens that can cause cancer include polychlorinated biphenyl congeners, pesticides, food-related mycotoxin zearalenone and its derivatives, ultraviolet screen, some metals, fungicides, algicides, oestrogens, retinoids, pyrethroid insecticides, pentachlorophenol, β -hexachlorocyclohexane, etc. Diet has influence on cancer development, and several compounds, either present as dietary components or contaminants or formed during food processing, may play a role in cancer risk. All these can adversely interfere with the physiological functions of oestrogens; mediate the hormonal responses by binding to oestrogen receptors; interact with steroid hormone binding proteins; inhibit oestrogen synthesis; and overall can interact with enzyme systems to modulate the oestrogen metabolism.

Keywords: Environmental and food contaminants, xenoestrogens, cancer.

INTRODUCTION

Cancer is an abnormal growth and proliferation of cells. It is a frightful disease because the patient suffers pain, disfigurement and loss of many physiological processes. Cancer may be uncontrollable and incurable, and may occur at any time at any age in any part of the body. It is caused by a complex, poorly understood interplay of genetic and environmental factors [1-7]. The lack of cell-cell adhesion and increased migration are key characteristics of cancer cells. All cancers occur due to activation or mutation of oncogenes, or inactivation of suppressor genes. More than 20 tumour suppressor genes and 50 oncogenes have been identified and characterized. Most of these genes are involved in activation and detoxification of polycyclic aromatic hydrocarbons (PAHs), suggesting a potential role of these compounds in carcinogenesis [8].

According to the WHO, cancer is the second largest cause of mortality and morbidity in the world after heart disease. 'Cancer' is a word that put an immediate emotional response, which have no relationship to rational thinking, depth of knowledge of the individual and role of individuals in the society. Such responses also occur in doctors, nurses, patients, families, friends of those who suffer from cancer, people who think they may have cancer, teachers, scientists, politicians, social workers and unskilled labourers, etc. Cancer rates continue to rise each year and it kills over 16 million people worldwide per year. However, in India the incidence of cancer may be as high as 3 million cases every year. In addition, more than 12,00,000 deaths occur every year from various types of cancer [8]. As per the other reports [9], cancer is the second leading cause of death in America; colon cancer is the second most common cause of cancer deaths and prostate cancer, second to skin cancer is the most frequently diagnosed cancer among men in the USA; while breast cancer is the most common of cancer in women worldwide. With increase in longevity, it is going to be a problem even in India. Cancers affecting the digestive tract are among the most common of all the cancers associated with aging. The major causes of cancer are smoking, dietary imbalances, hormones and chronic infections leading to chronic inflammation. It has been further stated [10] that cancer is one of the most dreaded diseases, and is leading cause of death; and presently in the USA, cancer accounts for 25% of all deaths in humans. Cancer kills annually about 3500 per million population around the world [2,9,11].

Oestrogens are the most commonly prescribed drugs by far the two major uses are as a component of oral contraceptives (OCs) and hormonal replacement therapy (HRT) in women. OCs used to control the birth, have influenced the lives of untold millions of women since they may cause cancer in humans as well as animals [2,12]. Due to wide use of OCs, a remarkable increase in cases of liver cell adenoma (benign or noncancerous tumour of liver) and hepatocellular carcinoma (HCC) have been reported [13]. There is evidence that long-term use of OCs may increase the risk of breast and cervical cancers. Many studies on animals demonstrate an increased incidence of various types of tumour with oestrogen, hence with the use of OCs. Vaginal, uterine and breast carcinomas have been caused by oestrogens [1-2,14-15]. The association between oestrogen use and cancer has been known for several years. 'Oestrogen cancer' hypothesis postulates that both exogenous and endogenous oestrogens and their metabolites play an etiologic role in the pathogenesis of cancer; and oestrogen administration is followed by regularly reproducible tumours of breast, uterus, ovary, pituitary gland, testicle, kidney and bone marrow either in mouse, rat, rabbit, hamster or dog [16]. Oestrogen can play a tumour-promoting role in target organs. This hormone is responsible for many illnesses in

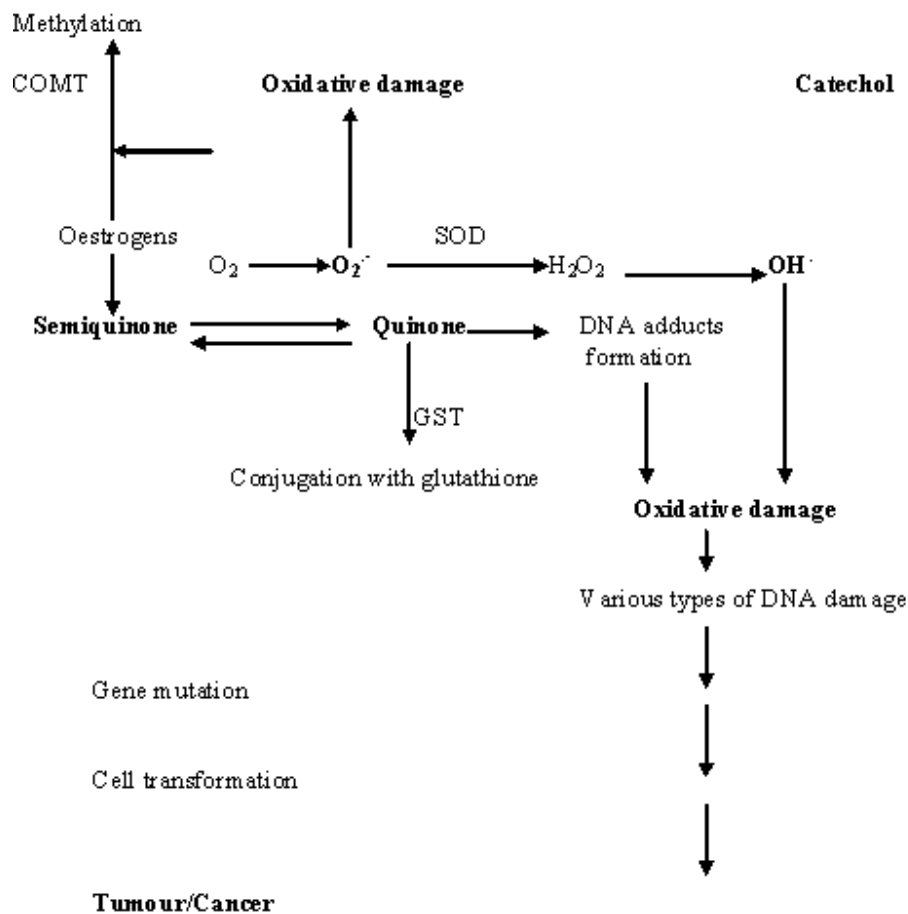
women as well as men [17]. Many reports [18] suggest that oestrogens are closely linked with the pathogenesis of breast cancer. This risk is increased with prolonged exposure by oestrogen; hence, early menarche and/or late menopause increase the risk. The age at first pregnancy, nulliparity, obesity, oestrogen replacement therapy or OCs are also related with the increased risk of breast cancer. The British and American studies [2,14] in women showed that oestrogen increased the risk of uterine (endometrial and cervical) cancer, and the women who begin menstruating early or who start menopause late, produce more oestrogen over their life times and have a higher risk of breast cancer. The natural oestrogens, viz., oestrone and oestradiol are recognized carcinogens in rodents and humans. Oestradiol increased the incidence of tumours of pituitary gland, mammary gland, uterus, cervix, vagina, testes, lymphoid system or bone in various strains of rats and mice [19-20]. In December 2000, the USA Government's National Toxicology Programme added oestrogen to the list of known human carcinogens [21]. It is disconcerting to think that a natural hormone (oestrogen) circulating in significant amounts through the bodies of about half of the world's population (women) is a carcinogen, but it is now official [22]. Ethinyl oestradiol (EO), a semisynthetic 17 β -oestradiol oestrogen, has been reported to cause cytotoxicity, leading to cancer in uterus, ovary and liver after prolonged administration in female albino rats [2,12]. Several reports [23] indicate that environment and food contaminants, including therapeutic agents such as antibiotics and antihypertensive drugs can cause various cancers. Further, the 'endocrine disruptors' influence the normal functions of oestrogens, thereby cause the cancer of several organs. The chemicals, industrial wastes, pesticides, OCs, detergents, food additives and plastics, all are sources of environmental toxins and endocrine disruptors. The potential endocrine disruptors such as antibiotics, hormones, plasticizers and non-ionic surfactants are becoming the priority pollutants; most of these have been shown to be carcinogenic [23-24].

With the above background, an attempt has been made through this review article to explore out certain xenoestrogens of environmental and food contaminants or hazards, leading to the development of many cancers.

Carcinogenic action of oestrogen

Oestrogens bind to cytoplasmic estrogen receptors (ERs) in oestrogen responsive tissues. The steroids-receptor complex then translocates to the nucleus, where it brings about changes in transcription. There are two types of ERs, viz., ER α (present in female genital tract, breast, hypothalamus, endothelial cell and vascular smooth muscle) and ER β (present in prostate, ovary and brain). Oestrogens act by interacting with specific ERs in the cytoplasm of target cells; this ER complex then translocates to the nucleus, where it attaches itself to the appropriate gene and mediates the transcription of relevant mRNA [1-2,6]. The differential expression of ER α or β during ovarian carcinogenesis, with overexpression of ER α as compared to ER β in cancer has been demonstrated [25]. This differential expression in ER suggested that oestrogen-induced proteins may act as ovarian tumour-promoting agents. After the oestrogen hormone binds to its receptors in a cell, it turns on hormone-responsive genes that promote DNA synthesis and cell proliferation. If a cell happens to have cancer-causing mutations, those cells will also proliferate and have a chance to grow into tumours. In carcinogenic oestrogen, the reactions produce intermediates capable of producing oxygen radicals that can damage the cell's fats, proteins and DNA. Unrepaired DNA damage can turn into a mutation, leading to cancer [2,12,14].

The oestrogen-induced carcinogenic mechanism has been fully explained [20]. Oestradiol may be converted to 4-hydroxyoestradiol or oestrone. If these catechol oestrogens are not detoxified by phase II enzyme activities such as catechol-O-methyltransferase (COMT), UDP glucuronosyl transferase or sulphotransferase, they may undergo metabolic redox cycling. Quinone or semiquinone intermediates in the redox cycle are free radicals, which generate more oxygen radicals and may induce various types of DNA damage. This genotoxicity may result in gene mutation and cell transformation. Thus, the tumours may develop from cells transformed by genotoxic action of oestrogen, which proliferate in response to an ER-mediated stimulus (Fig. 1).



O₂ : Superoxide free radical

OH : Hydroxyl free radical

Fig. 1: Proposed carcinogenic action of oestrogen

In the metabolism of xenobiotics, cytochrome P450 enzymes or monooxygenases catalyze hydroxylation reaction. This process occurs in two phases: cytochrome P450s 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 many molecules, e.g., glucuronic acid, sulphate, glutathione (GSH), acetyl or methyl groups, leading to excretion from the body. Several phase I and II enzymes are associated with oestrogen

metabolism [23]. Oestrogens are mainly hydroxylated by cytochrome P4501A1 (CYP1A1) and CYP1B1 into 2-hydroxyestrogens and 4-hydroxyestrogens, respectively [19,23]. It is believed that 4-hydroxyestrogens may act as a carcinogen [26]. In view of this, Mukherjee *et al.* [23] has explained the similar carcinogenic mechanism of oestrogen, as proposed by Liehr [20]. The metabolisms of 2- and 4-hydroxyestrogens (catechol oestrogens) are produced in a series of linked oxidation reactions that form the oxidative oestrogen metabolism pathway causing cancer. Such metabolism leads to 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. The superoxide radicals may be reduced to hydrogen peroxide and then to hydroxyl radical in the presence of metal ions. In general, quinones can be conjugated with GSH by glutathione-S-transferase (GST) or can form adducts with guanine and adenine base in DNA. The 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 potential. In addition, quinones and semiquinones undergo redox cycling which results in production of reactive oxygen species (ROS) that can cause oxidative damage to lipids, proteins and DNA. However, several phase II enzymes, e.g., COMT, GST and superoxide dismutase (SOD) participate in catechol metabolism (Fig. 1).

Environmental and food contaminants as carcinogens

Several factors have a major effect on increasing the rates of oral, colon, lung and breast cancers, etc. Some of these factors include increased infections, more use of pesticides, low consumption of fruits and vegetables, increased consumption of alcohol and red meat, more smoking, high industrial pollution, more exposure to sun, decreased physical activity and high occupational exposures. The major portion of chemicals to which humans are exposed is naturally occurring, that are carcinogenic at large doses. Almost every fruit and vegetable contains natural carcinogenic pesticides. Many natural chemicals are ingested as carcinogens from cooking food like roasted coffee. These include caffeic acid, chlorogenic acid, catechol, dichlorodiphenyltrichloroethane (DDT), furfural and benzo(a)pyrene, etc. A diet free of naturally occurring carcinogenic chemicals is impossible. Food additives (e.g., allyl isothiocyanate, alcohol, butylated hydroxyanisole and saccharin), mycotoxins (e.g., aflatoxin and hepatitis B virus) and synthetic contaminants (e.g., polychlorinated biphenyls and tetrachlorodibenzo-p-dioxin) are also mutagenic and carcinogenic [27]. The aryl hydrocarbons such as dioxins, polychlorinated biphenyls (PCBs) and PAHs bind to the cellular aryl hydrocarbon receptor (AhR); and activation of intracellular signaling subsequent to the AhR binding is highly correlated with the toxicity and carcinogenicity of these chemicals [28]. Humans are exposed to dioxins (belong to a group of halogenated aromatic hydrocarbons) mainly through contaminated foods. A dioxin compound, 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) is the most toxic congener. TCDD, benzo(a)pyrene and PCBs can activate AhR, which subsequently induce expression of CYP1A1 and CYP1B1 enzymes. Oestradiol is metabolized by these two enzymes, which activate benzo(a)pyrene to reactive DNA-binding intermediates. There is evidence of cross-talk between ER α and AhR-mediated signaling in breast and endometrial cells, thus the oxidative stress due to induction of cytochrome P450s is one of the toxic effects of dioxin [23].

Pesticides have become a part of environmental contaminants due to their widespread use in agriculture and disease control. Many pesticides are immunotoxic and found to suppress the cell-mediated immunity. Some of the selected pesticides are categorized as under: (a) insecticides

such as carbamate (carbaryl, carbosulfan, primicarb, methicarb, etc.), organochlorine (DDT, methoxychlor, aldrin, dieldrin, endosulfan, heptachlor, etc.), organophosphorus compounds (dichlorovos, malathion, parathion, chlopyrifos, trichlorfon, etc.) and pyrethroid (bioallethrin, deltamethrin, sumithrin, etc.); (b) herbicides such as amide (isoxaben, pentachlor alachlor, metolachlor, etc.), quaternary ammonium (paraquat, diquat, etc.), phenoxy (2,4-dichlorophenoxy acetic acid, 2,4-trichlorophenoxy acetic acid, etc.), trizine (atrazine, simazine, cyanazine, etc.) and unclassified group (oxadiazon, pentachlorophenol, etc.) [23]. The pesticides such as DDT and alachlor can behave like endogenous oestrogen and function to suppress apoptosis in ER-positive human breast cancer [29]. Some pesticides and related chemicals may act as carcinogens [30]. These xenobiotics have adversely affected the lymphocyte function [31] and increase oxidative stress and lipid peroxidation in various tissues [32].

Epidemiological studies indicate a close association between the process of westernization and an increase in breast cancer incidence. Western countries showed a higher breast cancer risk due to environmental influence. Besides reproduction-related factors, a westernized lifestyle is intimately associated with some particular food processing/cooking practices and dietary habits such as frequent use of fast foods. Thus the lifestyles, including oral or dietary habits are responsible for many cancers. Diet having several compounds, either as dietary components or contaminants or formed during food processing, has caused the cancer. Some dairy products such as whole milk and different cheese containing high levels of saturated fat, may increase cancer risk. Milk products also contain growth factor-I, which promotes breast cancer cell growth [33]. The intake of alcohol can increase the cancer risk by enhancing the levels of circulating oestrogen [34]. The food-related mycotoxin zearalenone and its derivatives such as α -zearalanol and β -zearalanol can bind to ER and exert oestrogenic action [35]. Zearalenone, a nonsteroidal compound produced by many *Fusarium* fungi species, can contaminate dairy products and cereals, e.g., barley, corn, maize, rice and wheat. This compound may be a potential promoter of breast tumorigenesis. 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. Nevertheless, there are some non-genotoxic carcinogens like chloropropanols (usually present in savoury foods). Furthermore, the N-nitro compounds, viz., N-nitrosamines and nitrosamides (e.g., N-nitrosureas) are a large group of chemicals that are linked with the pathogenesis of cancer. Humans are exposed to N-nitrosamines from a variety of foods and tobacco smoke. Interestingly, some pesticides like atrazine can be converted into genotoxic N-nitrosamines (N-nitrosoatrazine) in the environment or digestive system. PAHs are environmental contaminants formed during incomplete combustion of coal, oil, gas, garbage and other organic substances such as tobacco and different food items. Leafy vegetables can be significant sources of PAHs in the human diet. Benzo(a)pyrene is the best PAH compound available from diet. In general, PAHs occur in lower amount in cigarette smoke; human exposure is predominantly from dietary sources. Metabolic activation of PAHs results in DNA binding products. Cooking meat and fish at high temperature produces heterocyclic amines. Generally, heterocyclic amines are formed from creatinine or creatine, amino acids and carbohydrates. Thus, the higher consumption of meat is probably associated with an increased risk of breast cancer [23].

The westernized dietary habits, including smoking may increase the risk of breast cancer. Many lipophilic carcinogens of tobacco smoke, e.g., PAHs like benzo(a)pyrene, 4-aminobiphenyl and

N-nitrosamines can be stored in breast tissues. Some PAHs such as 7,12-dimethylbenz(a)anthracene (DMBA) and dibenzo(a,l)pyrene are potent mammary carcinogens [23]. Tobacco has unfortunately become a routine part of the personal environment in the world. It is the only legally available consumer product that kills people when it is used as directed. In India, 40% of total cancer cases are tobacco related. Almost one fourth of the India's population consumes tobacco. More than 10 million children below 15 years are addicted to tobacco. WHO links tobacco to 25 cancers, e.g., cancers of head, neck, lung, throat, urinary bladder, kidney, uterus and colon. In crowded environment, e.g., bar and restaurant, second hand smoke (passive smoke) can produce 6 times the pollution of a busy highway. Smoking includes bidi, cigarette, chutta, cheroot, pipe, cigar, dhumti, hookas, kalke, chillum, etc. Bidi has been said to be more harmful than cigarette. Smoke tobacco contains more than 4000 chemical compounds and at least 400 toxins, many of them are known carcinogens and irritants. Some airborne contaminants are PAHs, carbon monoxide, nitrogen dioxide and others. Tar (a mixture of many chemicals including formaldehyde, arsenic, N-nitrosamine, cyanide, benzopyrene, benzene, toluene and acrolein) and heavy metals (cadmium, arsenic, lead and nickel) may cause tobacco cancer. Many cancer promoters, initiators and accelerators as smoking agents are very potent carcinogens. These substances include nuclear aromatic hydrocarbons, chlorostilbenes, catechols, phenols and their substitutes, nitrosonornicotine, nicotine, cotinine nitrosamine and hydrazide [8].

Chewing materials of human beings include pan (betel); pan masala (a combination of areca nut, catechu, tobacco powder, aromatics, lime and brown or grey colouring agents); gutka; pan with tobacco (zarda, dokta or without tobacco); khaini; snuff; tobacco powder; areca nut; and naswar (a local preparation of Afghanistan commercially available as green tobacco powder mixed with calcium carbonate, calcium chloride, ammonium chloride, tobacco ignition residue, sand and other mineral substances). All these substances may increase the risk of oral cancer. Pan masala is unfortunately charged with polyaromatic hydrocarbons (especially dangerous proportion of magnesium carbonate), organochlorine pesticides (DDT and BHC), narcotics, metals and minerals. Heavy and regular consumption of alcohol is a significant risk factor for oral and other cancers. About 15% of oral and pharyngeal cancers may be attributed to dietary deficiencies or imbalances. Similarly, fungi (*Candida albicans*), viruses (human papilloma virus, hepatitis B virus, human T cell lymphotropic virus and human immunodeficiency virus), UV radiation, immunosuppression, certain occupations (farming and industries) and poor socio-economic status may develop the precancer lesions or carcinoma [8].

Endocrine disruptors (xenoestrogens) as carcinogens

'Endocrine disruptors' are xenobiotic (environmental/foreign) chemicals that adversely interfere with the natural functions of hormones [23-24]. Oestrogenic endocrine disruptors or xenoestrogen are widely distributed in the environment. Several chemicals such as polychlorinated biphenyl congeners, pesticides (e.g., dieldrin, endosulphan, pentachlorophenol), food-related mycotoxin zearalenone and its derivatives, ultraviolet screen, 3-(4-methylbenzylidene)-camphor and even some metals like cadmium can influence hormonal responses by binding to ER. The xenoestrogens interact with the binding pocket of the ER because they have chemical similarities to estrogen (usually a phenolic A-ring). Many xenobiotics can interact with the enzyme systems that metabolize oestrogens; and by this process they may modulate the endogenous metabolism. Numerous chemicals such as fungicides (e.g., fenarimol, procymidone, vinclozolin) and algicides (e.g., triphenyltin) inhibit steroid hormone

synthesis. Synthetic compound like diethylstilbestrol (DES) interfere the bio-availability and overall functions of oestrogen by interacting with steroid hormone binding proteins in the blood. The AhR or dioxin receptor has involvement with ER-mediated response pathways. Chemicals like retinoids, pyrethroid insecticides (e.g., sumithrin), pentachlorophenol and β -hexachlorocyclohexane alter steroid signaling pathways. Other man-made chemicals which can act as endocrine disruptors (related with oestrogens) include atrazine, DDT, EO, hexachlorophene and toxaphene, etc. These can influence the oestrogen functions, 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 [23].

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