Endocrine Disruptors, Adipose Tissue, and Obesity-Related Cancer

Maha Ahmad Abuhaimed, MD* Mohammed Alromayan, MD**

ABSTRACT

The endocrine system plays a crucial role in modulating the metabolism. Endocrine-disrupting chemicals (EDCs) are environmental chemicals that have been shown to interfere with the functioning of hormones. The aim of this literature review is to demonstrate the link between exposure to endocrine disruptors and the development of obesity-related cancer. Studies on the cancer-causing effects of EDCs focus mostly on those with estrogenic potential because the mammary gland and the uterus are the main estrogen target organs. In addition to their direct effects on the estrogen target organs, estrogenic EDCs may also indirectly increase or decrease the risk of developing cancer by affecting other risk factors. Human studies have showed inconsistency regarding the exact effect of EDCs and flame retardants on thyroid hormones. EDCs are known to mimic natural hormones and negatively affect the function and growth of normal reproductive organs.

Keywords: Adipose tissue; Cancer; Endocrine-disrupting chemicals; Neoplasm; Obesity

INTRODUCTION

The endocrine system plays a crucial role in modulating the metabolism of fats, proteins, and carbohydrates and ensuring that these fuels always meet the body's energy requirements. Hormones are responsible for storing excess fuel during times of plenty and mobilizing fuel during times of scarcity, as well as maintaining constant blood glucose levels. Any change to these hormonally regulated processes will likely result in a metabolic imbalance. The body's primary source of energy is fat stored in adipocytes (in adipose tissue), and it is now known that adipose tissue is also under the control of endocrine system and can function as an endocrine organ capable of hormone secretion[1]. Interference with the hormonal regulation of adipose tissue functions can result in abnormal fat deposition and, consequently, obesity.

The term endocrine-disrupting chemicals (EDCs) refers to a large number of environmental chemicals that have been shown to interfere with the functioning of hormones. Although the majority of research has focused on the disruption of reproduction due to interference with steroid hormone actions and interference with thyroid hormone actions[2,3], there are increasing reports that some EDCs can also interfere with the control of adipocyte function and regulatory processes in metabolism, leading to imbalances in the regulation of body weight (which can lead to weight gain)[4-6]. These chemicals are known as "obesogens"[7,8]. Obesogens may have a negative impact on body weight and lipid balance in different pathways including alterations in adipocytes size, thyroid and hypothalamic glands regulations of metabolism, insulin sensitivity and other mechanisms[9]. Furthermore, obesogens were found to have an impact at a cellular level as they can disrupt steroidal receptors and PPA receptors (peroxisome proliferator-activated receptors)[10].

In recent decades, an increase in obesity, defined as a body mass index greater than 30 kg/m2, has become a global problem. Over 20% of adults in the United Kingdom and over 30% of adults in the United States are now obese[11]. In addition, childhood obesity is on the rise in westernized nations; in the United States, approximately 20% of children (aged 3 to 17) are obese[11]. Although there are genetic determinants that contribute to inherited susceptibility and environmental influences from excessive food consumption and lack of exercise in modern life, these factors alone cannot explain the current disease trends. As obesity, adipose tissue, and endocrine disruptors are interrelated factors that may promote the development of cancers associated with obesity. The aim of this literature review is to demonstrate the link between exposure to endocrine disruptors and the development of obesity-related cancer.

2. ENDOCRINE-DISRUPTING CHEMICALS

Endocrine disruptors are substances or mixtures of substances that can be absorbed by the body and interfere with normal hormone function[12]. Endocrine disruptors were defined by the U.S. Environmental Protection Agency (EPA) as “an agent that interferes with the synthesis, secretion, transport, binding, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development and/or behaviour”[13]. Furthermore, the substance is referred to as "Potential endocrine disrupter" if it possesses properties that could possibly lead to endocrine disruption. Although most EDCs are synthetic, some come natural sources[14,15]. The timing and length of EDCs exposure are critical factors in the determination of the resulting effects on the endocrine system due to their similarity to the natural endocrine hormones in have varying effects at various points in the life cycle[16]. Endocrine disruptors can lead to hormonal imbalances due to their interference with the endocrine system. EDCs can exhibit various mechanisms of action, such as binding to a hormone receptor to inhibit or activate its signaling pathway, interacting with hormone signaling pathway components downstream of a receptor, stimulating or inhibiting endogenous hormone biosynthesis, stimulating or inhibiting hormone-binding protein synthesis or degradation, binding to circulating hormone-binding protein, and stimulating or inhibiting hormone receptor expression[17]. Other toxicological mechanisms may possibly have additional negative consequences in molecules with known endocrine disrupting activities. They may be teratogenic or genotoxic (alteration of DNA: either by epigenetic modifications or by mutations), which may result in malignancies apart from endocrine-

* Family medicine
Riyadh second health cluster,Ministry of health, Riyadh, Kingdom of Saudi Arabia
Maabuhaimed@moh.gov.sa
Mahaabuhaimed1@gmail.com
** General, Bariatric and GI surgery
Security Forces Medical City,
Riyadh, Kingdom of Saudi Arabia
Maalromyan@moi.med.sa

related cancers, or directly cytotoxic or reprotoxic (direct alteration of gametogenesis or other reproductive stages)[18]. For instance, BPA shows cytotoxic and genotoxic effects that have nothing to do with its EDC characteristics[18-20]. The aryl hydrocarbon receptor (AhR), which dioxin acts as an EDC via, has also been demonstrated to be a powerful genotoxic[21]. The possibility must be considered even though these cytotoxic and genotoxic effects are often seen at higher concentrations than endocrine-disturbing effects.

2.1 Types of Endocrine Disruptors

EDCs are widely distributed in nearly everyday objects used by humans as the exposure could be through ingestion, air inhalation and even dermally through products used daily such as plastics, the lining of cans, toys, personal care items like sunscreen, household detergents and pesticides[22]. EDCs have a lipophilic nature and thus they bioaccumulate in the adipose tissue of living organism and become difficult to eliminate once they have entered the food chain[23]. Moreover, humans are exposed to many different EDC-containing products every day at low doses which has become acceptable worldwide[24]. However, there are certain times in which the exposure is more critical and can produce irreversible effects. EDCs exposure during pregnancy has the potential to produce transgenerational consequences which can be the base for future disease later in life[25]. Chemicals that disrupt the endocrine system can be categorized according to their lipophilicity. The terms "persistent organic pollutants" (POPs) refer to substances with a long half-life and a high lipophilic activity that can bioabsorb in fat and bioamplify via the food chain[26]. Dioxins, heptachlor, dichlorodiphenyl-trichloroethylene, and polychlorinated biphenyls are representative chemicals. Numerous epidemiologic and in vitro investigations have estimated the gynecologic health risks to human populations posed by POPs[27-30].

Other substances with a shortened half-life and reduced lip solubility are known as non-persistent EDCs (npEDCs)[26]. Bisphenol A (BPA), triclosans (TCSs), phthalates, and parabens are examples of npEDCs. BPA is a common EDC found in infant bottles, dental sealants, children's toys, receipt coating, and epoxy resins used to coat the interior of food cans. Di-2-ethylhexyl phthalate (DEHP) is a plasticizer used in a variety of products, including plastics, cosmetics, and medical devices. In personal care products such as cosmetics and pharmaceuticals, parabens are used as preservatives[26].

EDCs are incredibly diverse[31,32]. They may be divided into two classes[33]:

(i) Those occurring naturally. Phytoestrogens, such as genistein and coumestrol, are naturally occurring chemicals present in human and animal foods.

(ii) Substances synthesized. These can be categorized further as follows:

- •Synthetic compounds used as industrial solvents or lubricants and their by-products (for example, polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dioxins)
- •Plastics (such as bisphenol A)
- •Plasticizers
- •Pesticides (such as dichlorodiphenyltrichloroethane)
- •Fungicide (e.g. vinclozolin).
- •A number of pharmaceutical agents, including diethylstilbestrol (DES).

The EDCs can also be categorized based on their origin[34]:

(i) Natural and synthetic hormones (such as fitoestrogens, 3-omegafatty acids, contraceptive tablets, and thyroid medications).

(ii) Medications that cause hormonal adverse effects, such as naproxen, metoprolol, and clofibrate.

(iii) Industrial and household chemicals, such as phthalates, alkylphenoletoxilate detergents, flame retardants, plasticizers, solvents, 1,4-dichlorobenzene, and polychlorinated biphenyls (PCBs).

(iv) By-products of industrial and domestic processes, including polycyclic aromatic hydrocarbons (PAHs), dioxins, and pentachlorobenzene.

Since EDCs are very similar to hormones and have the capacity to function at low concentrations, they may interfere with hormone activity in one of two ways[17]:

1) Directly acting on the hormone-receptor complex (activation or inhibition effect).
2) Affecting a particular protein that regulates certain parts of the hormone delivery process (altering hormone bioavailability).

More details regarding EDCs modes of action are listed in Figure 1.

2.2. Nonmonotonic response and cocktail effect

The adverse effects of EDCs exposure may not be fully predicted as the high toxic doses observations do not give precise estimation of the potential low doses impact on the living organism. This phenomenon is related to EDCs having a nonmonotonic dose response curve (Non-linear) similar to the effects produced by normal hormones[35,36]. When humans are exposed to simultaneous low doses of EDCs via different routes, their cumulative and combined effect (cocktail effect) results in clinical damage years later rather than showing immediate consequences[37].

3. ENDOCRINE DISRUPTING CHEMICALS AND ADIPOSE TISSUE AND OBESITY

3.1 Endocrine Disrupting Chemicals and Obesity

An abnormal or excessive accumulation of fat that poses a health risk characterizes overweight and obesity. Overweight is defined as a body mass index (BMI) greater than 25 kg/cm2, and obesity is defined as a BMI greater than 30 kg/cm2[38]. In 2017, more than four million individuals per year died as a result of being overweight or obese[38]. Adipose tissue, also known as body fat, is necessary for the production of hormones and storage of energy. Adipose tissue accumulation, however, can contribute to obesity. The fundamental cause of obesity

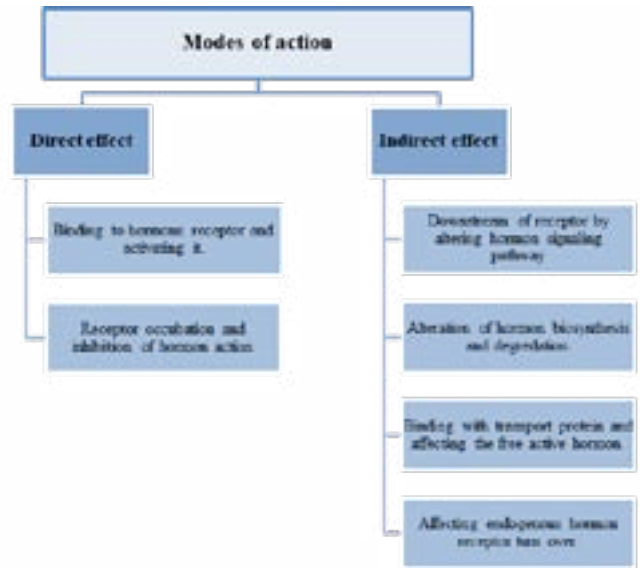

Figure 1. EDCs modes of action

is a chronic energy imbalance between excessive caloric intake and insufficient caloric expenditure[39]. The risk of metabolic diseases, cardiovascular diseases (myocardial infarction, hypertension, and stroke), osteoarthritis, depression, Alzheimer disease, and certain types of cancer (such as prostate, breast, ovarian, liver, kidney, and colon) significantly increase among obese people[40].

The endocrine system is essential for controlling how lipids, carbs, and proteins are metabolized and ensuring that these fuels always satisfy the body's energy needs[3]. In addition to regulating blood glucose levels, hormones are in charge of storing extra fuel during times of abundance and mobilizing it during times of scarcity. Any modification to these hormonally controlled procedures will probably cause a metabolic imbalance[3]. The body uses fat stored in adipocytes in adipose tissue as its main source of energy; nevertheless, it is now understood that adipose tissue is also under endocrine control and can serve as an endocrine organ capable of secreting hormones[1]. Therefore, aberrant fat accumulation and, as a result, obesity can also develop from hormonal interference with adipose tissue processes. Endocrine disruptive substances or endocrine disruptors are a broad category of environmental chemicals[12]. Despite the fact that most studies have concentrated on the interruption of reproduction brought on by interfering with the functions of thyroid hormones and steroid hormones[12], EDCs can also disrupt the control of adipocyte activity and metabolic regulatory systems, causing abnormalities in the regulation of body weight that can result in obesity[5,6,41].

EDCs and Adipose Tissue Adipose tissue (AT) is a major contributor to toxicological responses to EDC exposure, particularly to POPs with a predominantly halogenated structure, which renders them non-metabolizable and exceedingly lipophilic[42]. Since EDCs are released gradually or in huge amounts during lipolysis, AT is really regarded to be the main internal source of long-term, low-level systemic exposure to these compounds, despite the fact that it may appear to perform a protective role by storing POPs. Thus, AT serves as a dynamic storage compartment for EDCs in the body, with a constant flow between storage and release throughout post-exposure periods. PCBs have been examined in a lipolysis-imitating mouse cell model[43], the dynamic mobilization of EDCs by AT has been the subject of several in vitro and in vivo studies. Others have shown that TCDD deposited in AT of xenograft can be released into recipient animals and affect gene expression, offering a direct proof of the potentially detrimental effects of TCDD. This was done using a xenografted fat model[44]. A considerable weight loss is associated with prolonged release of POPs from AT, primarily hexachlorobenzene and PCB-153, DDE, in the first year following bariatric surgery[45]. Despite consensus on the prevalence of some EDCs and their relationship on metabolic parameters, adipocyte size, and AT macrophage infiltration[46,47], investigations have also been made into the unique variations in EDC bioaccumulation that occur in the fat depot. Contradictory outcomes, though, have been found thus far.

The AT serves as a full-fledged endocrine organ, producing and regulating hormones and adipokines in addition to serving as a storage organ[48,49]. Adipocyte differentiation, adipocytokine production, oxidative stress, and inflammation are only a few of the EDCs whose substantial effects on AT physiology have been documented in vitro and/or in vivo[50-52]. EDCs have been referred to as obesogens based on a number of papers that have shown a potential function for them in the origin of obesity[48,50,52-54]. In fact, AT experiences two morphological changes when exposed to chronically high calorie intake: hyperplasia (growth in adipocyte number) and hypertrophy (increase in adipocyte size due to lipid build-up in the adipocytes)[48,55]. In a healthy AT expansion, hyperplasia occurs. However, hypertrophy results in the production of dysfunctional adipocytes, which secrete pro-inflammatory adipocytokines including TNF-alpha, MCP-1, IL-6, and IL-8, as well as adiponectin, leptin, or resistin as the primary ones. Adipocyte mortality via membrane rupture and the release of cellular content into the microenvironment are both caused by hypertrophy, which also increases hypoxia and decreases vascular supply. All of this leads to the invasion of inflammatory immune cells, such as lymphocytes and granulocyte type 1 macrophages, changing the microenvironment of the AT and causing the development of crown-like structures. Reactive oxygen species (ROS) produced by certain structures are likely to cause DNA damage. Local metabolism as well as systemic energy homeostasis are both impacted by this low-grade chronic inflammation. EDCs can influence adipose secretion in addition to AT hypertrophy and hyperplasia[42,56,57]. For instance, because PPAR is a crucial molecule in the control of adipogenesis, any EDC that acts as an agonist on this receptor is likely to result in the expansion of adipocytes, which will change the secretome and make it an obesogenic EDC. PFOA[58-62] and tributyltin (TBT)[54] are two examples. TBT has been demonstrated to increase fat mass and stimulate inflammatory infiltration into adipocytes as well as the reproductive tract[63-65]. Some EDCs induce adipogenesis by means of estrogen, glucocorticoid receptors, or other mechanisms in addition to binding to PPAR. Furthermore, studies on murine and human adipocyte cells and on TCDD in mouse AT have demonstrated the pro-inflammatory effects of several EDCs, including dioxins, through the AhR pathway[66,67]. In addition to in vitro and in vivo investigations, a number of epidemiological studies support the idea that transgenerational effects on progeny can result from prenatal or postnatal exposure to EDCs and elevated BMI[50,52,54,68]. EDCs may thus cause abnormalities in local and systemic energy metabolism as well as an inflammatory response if they interfere with the coordinated control of adipocyte metabolism, growth, and endocrine function[69]. EDCs' effects on the endocrine function of adipocytes have been studied, but primarily in relation to obesity and/or cardiometabolic diseases.

Obesogens are substances (such as EDCs) that can induce obesity in both humans and animals. Numerous studies have demonstrated a causal link between EDC exposure and the onset of obesity in model organisms, whether directly or indirectly by increasing sensitivity to factors such as a high-fat diet. Numerous EDCs renowned for their obesogenic effect on animals are associated with an increase in obesity prevalence[70]. Obesogens can directly affect adipocytes to increase their number, encourage fat storage in already-existing adipocytes, or generate adipocytes that are dysfunctional. By altering metabolic set points, causing unfavourable changes in the composition of the microbiome, altering metabolic set points, and increasing the proportion of calories consumed that are stored as fat, among other mechanisms, obesogens can also indirectly increase adiposity[50,54,71].

When exposure takes place during crucial developmental windows, sensitivity to the obesogenic effects of EDCs is especially high. This is due to specific characteristics of the fetus and new-born, such as reduced expression of the cytochrome P450 enzymes that metabolize xenobiotics, that result in higher tissue exposure than adults[72]. A wide range of processes are also controlled by hormone signalling pathways in the early years of life, when they can respond to and adapt to physiological stresses[70]. This ability also makes people more vulnerable to environmental stressors like EDCs, which can change several systems over time and raise the chance of becoming obese later in life. In fact, exposure to obesogens in infancy may alter physiological functions that are important regulators of body mass, such as appetite regulation, energy metabolism, and adipogenesis, resulting in a frugal phenotype and raising the risk of weight gain.

Numerous animal and epidemiological studies have proven that early-life exposure to EDCs has an obesogenic effect. BPA[73], insecticides[74],

nonylphenol[75], and PFOA[76] have all been linked in rodent studies to prenatal or early postnatal weight gain, with a dose- and gender-dependent relationship. Human studies have also demonstrated a link between prenatal EDC exposure and a higher risk of obesity in adulthood[70]. Animal model studies suggest that several EDCs also have obesogenic effects when exposure takes place after crucial developmental periods, which is vital to note[74]. As a result, in the case of ongoing exposure, it is most likely that the effects of exposure during infancy and maturity eventually define how obesogens affect phenotypic. However, little is understood about how exposure to diverse historical periods interacts.

Early-life obesogen exposure can increase white adipose tissue mass by augmenting the steady-state number of adipocytes or adipocyte precursors. It also promotes the development of adipocytes from multipotent mesenchymal stromal stem cells or existing preadipocytes. The activation of specific nuclear hormone receptors by EDCs has been extensively studied as the mechanism underlying the action of obesogens due to its ability to alter fat cell commitment, differentiation, and function. Because it is additionally referred to as the "master regulator" of adipogenesis, the nuclear receptor PPAR is a plausible candidate for explaining the obesogen activity of compounds[77]. As with other PPARs, PPAR has to heterodimerize with RXR in order to bind DNA and control its target genes. Adipogenic genes are expressed more frequently when this heterodimer is activated by endogenous ligands, medications, or EDCs, which results in the development of fat cells. In order to stabilize and advance the adipogenic destiny, PPAR interacts reciprocally with the transcription factors CCAAT-enhancer binding proteins (C/EBP)[78]. Because of this, PPAR was the focus of numerous screening attempts to find possible obesogens[79-81]. Using screening techniques like adipogenesis inducers in human cell-culture models by activating PPAR, such as lactofen, diclofop-methyl, and MEHP, a range of real and potential chemical obesogens have been discovered[82]. However, it is known that PPAR-independent processes may be used by EDCs to cause adipocyte differentiation. This is the case for polychlorinated biphenyls (PCBs), organophosphate insecticides, bisphenol A, and nicotine, all of which enhanced adipogenesis through processes that may not have directly included PPAR activation[78,83]. In 3T3-L1 preadipocytes, PCB-77 promotes adipocyte development via the aryl hydrocarbon receptor[66].

It's noteworthy that some obesogenic effects don't seem to be affected by nuclear hormone receptor modulation directly. These include the obesogen's transgenerational effect or the transmission of the fat phenotype to future generations after exposure to the chemical during infancy[84]. Understanding these transgenerational effects, which have been observed for a small number of chemicals, has been a major focus of research; probable hypotheses include chromatin architectural changes and epigenetic modifications[84].

3.2 The Impact of Endocrine Disrupting Chemicals on Adipose Tissue

Due to their ability to imitate hormonal functions, EDCs can have a wide range of impacts. The nuclear hormone receptor superfamily, which includes steroid hormone receptors, thyroid hormone receptors, retinoid X receptors (RXR), peroxisome proliferator-activated receptors (PPAR), liver X receptors, and farnesoid X receptors, is the mechanism of action for the bulk of the EDCs investigated[85,86]. All nuclear receptor ligands have two traits in common: small size and lipophilicity. It is hardly unexpected that many EDCs possess these traits. For example, it is well known that activation of the nuclear hormone receptor PPAR encourages the development of fat cells[87]. The expression of genes associated with adipogenesis, glucose, lipid, and cholesterol metabolism is controlled by the dimerization of PPARs with RXR and their binding to PPAR-responsive DNA regulatory elements[88]. In light of PPAR's physiological role in the synthesis and maintenance of adipose tissue, it has been proposed that disruption of the regulatory pathways regulated by PPAR may play a role in the emergence of obesity and other metabolic disorders[89]. Natural PPAR ligands that promote the expression of genes and enzymes involved in lipid metabolism include poly- and monounsaturated fatty acids, eicosanoids, and lipophilic hormones[88]. Perfluorinated chemicals (PFCs), certain phthalates, and variants of bisphenol A (BPA) all bind to and activate PPAR. By encouraging the differentiation of preadipocytes into mature adipocytes, the aforementioned xenobiotic substances that activate this receptor enhance adipogenesis both in vitro and in vivo[89].

3.3. Endocrine Disrupting Chemicals and Hormone Sensitive Cancers

Cancer is a broad category of diseases that can affect any organ or tissue in the body. Also included are malignant tumors and neoplasms[90]. Cancer is characterized by a rapid growth of abnormal cells that attack neighboring tissues and spread to other organs, a process known as metastasis. The primary cause of cancer-associated mortality is widespread metastases[90]. Cancer accounted for nearly 10 million deaths worldwide in 2020[91], making it the primary cause of death worldwide. In 2020, the most prevalent forms of cancer were breast, prostate, non-melanoma skin, lung, colon and rectum, and stomach. Cancer is the consequence of the transformation of normal cells into cancer cells through a multistep process that typically moves from precancerous lesions to malignant tumors[90]. These modifications are the result of the interaction between a person's genetic factors and three types of external agents: chemical carcinogens (such as alcohol, aflatoxin (a food contaminant), asbestos (components of tobacco smoke), and arsenic (a drinking water contaminant)), physical carcinogens (such as radiation), and biological carcinogens (such as infections)[90].

It is believed that a number of cancers are caused primarily by hormones that are assumed to circulate regularly in the body and connect to the membrane and/or nuclear receptors of cancer cells, promoting cancer cell growth and division. Along with breast cancer (BCa), which is the most common cancer in women worldwide, prostate cancer (PCa) and endometrial cancer (ECa), two of these hormone-dependent malignancies, are the most common cancers of the male and female reproductive systems, respectively[92]. In the genesis, progression, and treatment of hormone-dependent cancers[93-95], steroid hormones (estrogens and androgens) play a significant role. Therefore, it follows that exposure to EDCs can affect the occurrence and progression of certain cancers[96].

EDCs (including diethylstilbestrol) were originally recognized as a risk factor[57]. In order to lower the risk of abortion, pregnant women were frequently provided with this synthetic diphenol until the 1970s; nonetheless, some investigations have found an elevated risk of uncommon malignancies in female offspring[57,97]. It is significant because the harmful consequences of prenatal DES exposure have been demonstrated to last into the second generation, opening the door for the idea of epigenetic transgenerational inheritance[98]. After that, a number of epidemiological studies backed by in vivo and in vitro tests have established this link between EDCs (namely PCBs, DDE, dioxins, and bisphenol A [BPA]) and a higher risk of hormone-dependent malignancies in both genders[68,99-101]. BPA can promote seminoma cell proliferation via the GPR30/GPER pathway in cases of testicular cancer[102-104]. Prins et al.'s research on PCa has demonstrated that exposure to BPA increases the sensitivity of prostate stem cells to estrogen in adulthood and increases the likelihood that

PCa will manifest[105,106]. Exposure to chlordecone is a demonstrative example of persistent EDCs, even though it has been highlighted, as it significantly raises the risk of PCa and recurrence following radical prostatectomy[107,108]. An industrial organochlorine compound called PCB-153 may play a role in the emergence of high-grade PCa[109]. The plasma concentrations of PCB-153 and PCa, however, showed an inverse relationship in a prior investigation[110]. Studies also disagree on whether increased blood PFOA levels are associated with the initiation or progression of PCa or not[61,111]. As a result, despite the substantial research on the part of some EDCs in the occurrence of hormone-sensitive malignancies, many investigations of their mechanisms of action, their effects on tumor growth, and their impacts on the development of metastases, particularly in humans, are still not fully understood[68,112].

3.3.1 Estrogen Dependent Female Carcinogenesis

The most prevalent female gender-related neoplasms whose growth is predominately estrogen dependent are breast and uterine cancer[113]. Therefore, the risk of these two estrogen-dependent cancers may be increased by any EDC demonstrating estrogenic actions. The findings of a large number of rat studies highlight the significance of pre-pubertal and prenatal exposure to EDCs in the etiology of breast and uterine cancer[114,115]. Altering the hormonal environment during pregnancy and before puberty can have negative impacts on adult uterine and breast morphology and function[116]. According to the so-called somatic mutation theory (SMT), the process of carcinogenesis is typically viewed as the result of DNA mutations in the genes that regulate cell proliferation, differentiation, and maturation[117]. The so-called tissue organization field theory (TOFT), which was proposed recently, contends that cell-to-cell communication and cell-matrix interactions play a crucial role in the disturbance at the tissue level that leads to malignancy when these interactions go wrong[118]. The stroma and epithelium interact often throughout breast tissue development; hence, the TOFT is more likely to account for the etiology of breast cancer[119]. The stroma of the developing mammary gland is the only tissue compartment where fetal expression of the two ERβ and ERα isoforms has been identified[120,121], highlighting the importance of this tissue compartment in the normal development of the breast. Consequently, any imbalance in the hormonal and growth factor exposure that regulates how the stromal and epithelial tissue of the developing mammary gland develops correctly may cause neoplasia later in life. This connection is extensively supported by experimental findings from developing breast tissue in rats and mice[119].

3.3.1.1 Direct effects of EDCs on the development of estrogen dependent cancer

Studies on the cancer-causing effects of EDCs focus mostly on those with estrogenic potential because the mammary gland and the uterus are the main estrogen target organs. Since BPA is the most common estrogenic EDC present in numerous consumer products[122-124], the majority of data comes from studies on this substance. The actions of BPA on cell lines that express ERs, such as MCF-7, simply demonstrate its estrogenic qualities and do not necessarily indicate that it has carcinogenic potential[122]. Data from numerous studies using breast cancer animal models, however, suggest that BPA may potentially encourage the establishment of this malignancy through non-estrogen-dependent mechanisms[122,125]. Additionally, it has been emphasized that the timing of this compound exposure has a significant impact on breast cancer risk[126]. This malignancy appears to be greatly influenced by interactions with the peri-ductal stromal breast tissue during fetal mammary gland development[127]. Clinical evidence on the risk of breast cancer development as a result of estrogenic EDC exposure is scarce and contradictory[128-131]. However, it was recently shown in research by Cohn et al. that in utero exposure to the estrogenic pesticide DDT is linked to an elevated risk of breast cancer in later life[132].

Surprisingly, there is relatively little information on how EDCs contribute to the development of uterine hyperplasia and cancer. Hiroi et al. carried out the initial investigation into how EDCs affect females' endometrial morphology[133]. These scientists showed that there may be a link between BPA exposure and estrogen-dependent endometrial diseases. However, Sturgeon et al.'s investigation found no evidence of a connection between endometrial cancer and DDT-related substances, PCB congeners, or organochlorine compounds[134]. Surprisingly, research on dietary isoflavones has found that females have a lower chance of developing endometrial cancer[135,136], but evidence from animal studies suggests that plant-derived compounds and their estrogenic metabolites may have uterotrophic potential. For instance, it has been demonstrated that the soy compound equol, a metabolite of daidzein, increases endometrial size and hyperplasia in ovariectomized rats[137]. These findings were in line with research by Unfer et al. which found that endometrial hyperplasia was more common in females receiving soy extracts than in those taking a placebo to treat menopausal symptoms[138]. There is still a need for research on the relationship between estrogenic EDC exposure and the risk of endometrial hyperplasia and cancer.

3.3.1.2 Indirect effects of EDCs on the risk of estrogen dependent cancer

In addition to their direct effects on the estrogen target organs, estrogenic EDCs may also indirectly increase or decrease the risk of developing cancer by affecting other risk factors. Late menopause and early menarche increase a female's lifetime estrogen exposure, increasing her chance of developing cancers that are estrogen-dependent[139]. Therefore, any EDCs that have an impact on these two life events for females may also have a sizable impact on the likelihood of developing breast and uterine cancer[113,140]. There is a severe lack of conclusive information from human research that relates exposure to EDCs to age at menarche. In utero exposure to dichlorophenyldichloroethylene (DDE) decreased the age at menarche by one year[141]. This link was no longer significant when the anticipated body size at menarche was taken into account. Similarly, adolescent females with moderate urine BPA concentrations were less likely than those with the lowest to experience early menarche. Additionally, the link between urine BPA concentrations and menarche age was significantly affected by overweight status[142]. There is still a dearth of clinical information about the impact of EDC exposure and the timing of menopause.

EDCs that interact with ERs or estrogen signaling pathways may also indirectly impact the risk of estrogen-dependent cancer through their effects on the hypothalamic-pituitary-gonadal axis. In the hypothalamus, EDCs with anti-estrogenic characteristics increase ovarian steroid production and gonadotropin release. This increases exposure to high levels of unopposed estrogen. On the other hand, EDCs with estrogenic effects may also lead to an ongoing rise in LH (a "positive" feed-back loop), which results in an excessive amount of androgen being produced by the theca cells—a trait typically observed in women with PCOS[143]. The results of numerous clinical trials support this theory. Unovulatory infertility and uterine cancer risk are both increased in PCOS-affected females [144]. However, there is still a lack of consistency on the risk of breast cancer[145].

Another factor that significantly affects the risk of uterine and breast cancer is obesity[146,147]. This connection is caused by the dysfunctional overexpression of the aromatase enzyme in adipose tissue, which causes androstenedione to be converted from the adrenal cortex into estrone, which can then be turned into E2 by the activity of

Figure 2. Main mechanisms associating obesity and cancer[159]

the 17-hydroxysteroid dehydrogenase, resulting in unopposed hyperestrogenemia[148]. As a result, variables that promote or encourage obesity can also significantly affect the risk of breast and uterine cancer, particularly in postmenopausal females. Recent research has provided evidence that prenatal exposure to EDCs is linked to the later development of obesity[149]. Additionally, it has been demonstrated that eating foods high in persistent organic pollutants (POPs) increases obesity, which in turn affects the chance of developing breast cancer[150]. The obesogenic potential of this EDC is also indicated by data from research on the metabolic effects of BPA[151].

Prolactin (PRL), the hormone that triggers postpartum breastfeeding, also acts on breast tissue as a target organ. The action of estrogens and their signaling pathway is primarily responsible for the pituitary lactotrophic cells' synthesis of PRL. Because of this, any EDC with estrogenic action may cause PRL secretion. Animal tests have actually supported this[152,153]. It is currently unclear if exposure to high PRL levels increases the chance of developing breast cancer[154]. The primary organ that PRL acts on is the breast tissue, where it promotes maturation and growth both postpartum and during puberty[155]. Therefore, such a relationship is justified. However, there is still a dearth of clinical information about how exposure to EDCs in humans affects PRL secretion[101].

3.3.2 Obesity-related cancers

As risk factors—primarily obesity and metabolic syndrome—become more prevalent, cancer incidence is continuing to rise[156]. In practically all countries the incidence of obesity has drastically increased, reaching epidemic proportions in industrialized nations where it affects 60–70% of the adult population[157,158]. When excess energy consumption outpaces metabolic and physical activity-related energy expenditure, obesity develops[159]. Ectopic fat tissue forms as a result of excessive or aberrant fat tissue deposition that surpasses the genetically and epigenetically specified adipose tissue stores, which increases the risk for several disease types. The growing incidence and prevalence of cancer are mostly determined by obesity \[160]. Ectopic fat deposition can alter DNA repair, gene function, cell mutation rate, and epigenetic regulation, which can lead to the development and spread of cancer[161,162]. These changes can be brought on by a variety of metabolic, inflammatory, and immunologic factors, Figure 2.

Because EDCs can interfere with hormones working inside the human body in many ways, EDCs build-up in human body was found to cause adverse health effects such as infertility, impaired sexual development, alterations of thyroid or adrenal glands function, increased risk for certain malignancies, immunosuppression and autoimmune disease[163]. Previous in vitro and in vivo studies have demonstrated the adverse effects, that could be permeant, of the accumulated low doses of EDCs on human body specially when taken at early stage of life (prenatal), specially on the reproductive system and sexual hormones[164,165].

3.3.2.1 EDCs and Breast Cancer

The biological consequences of PFAS exposure are primarily investigated in rodents, and the major impacts on humans have not yet been thoroughly investigated. Recent epidemiological data, however, describes the link between PFAS exposure and the emergence of breast cancer. For instance, PFOA may raise the chance of developing breast cancer and interfere with development[166-168]. In addition, a study of Inuit females in Greenland found that breast cancer risk was higher in females with higher blood serum levels of PFOA, PFOS, and other

PFAS chemicals[169,170]. Similar findings were found in a cohort study of French females, which linked circulating PFAS levels to an increased risk of breast cancer. Particularly, low concentrations of circulating PFOA and PFOS were linked to cancers that lacked the estrogen receptor, while circulating PFOS concentrations were linked to tumors that did[171].

A recent study found that young Taiwanese females exposed to PFAS had an increased chance of developing breast cancer. More specifically, the risk was higher in females under 50 and rose when tumors expressed the estrogen receptor[172]. Exposure to PFAS is linked to breast cancers that lack hormone receptors. Perfluorohexane sulfonate (PFHxS) exposures were linked to an elevated risk of hormone receptor-negative breast cancer[173]. The serum PFOS levels and breast cancer were also found to have a strong positive connection in studies on Danish pregnant women. In a follow-up study, scientists examined polymorphisms in genes involved in the metabolism of estrogen, as well as environmental endocrine disruptors, and found that exposure to PFOS was more strongly linked to breast cancer risk in females who had some of these changes in these genes[174,175].

There is also epidemiological data connecting paraben exposure to breast cancer growth. Breast tissue, particularly breast tumor tissue, has been found to contain parabens[176-179]. Parabens have also been identified in breast cancer patients' urine and plasma samples[180]. Despite the fact that plasma paraben levels seem to be greater in females with breast cancer, few epidemiological research have linked paraben exposure to an increased risk of breast cancer[181]. Females who had urine total paraben levels in the highest quintiles had a 35% higher risk of breast cancer[182]. However, there is an inverse connection between total paraben exposure and breast cancer risk in postmenopausal females[183]. The results of these two studies are difficult to compare because one study[182], which gathered postdiagnostic urine samples, and the other[183], which collected prediagnostic urine samples. Studies that looked at the relationship between using personal care products (representing a potential source of parabens) and the risk of breast cancer reported conflicting findings, with the Norwegian females reporting a weak inverse association[184] and the Sister Study finding a 10% to 15% higher risk of breast cancer in females who used beauty products moderately to frequently compared to females who used them less frequently[185].

In Vivo Evidence

Animal models are being used in more studies to determine how parabens affect health outcomes. Rodents exposed to PFOA are more likely to develop their mammary glands later, have smaller babies, and have neonatal deaths[168,186]. Additionally, PFAS exposure can affect the development of the mammary gland in female CD1 mouse pups and impair nursing in mothers[168].

According to Mogus et al., exposure to propyl paraben during pregnancy and breastfeeding causes an alteration in the immune cell profile in the mammary gland as well as an increase in epithelial cell proliferation and a decrease in collagen thickness[187]. Although these findings imply that propyl paraben can have a considerable impact on the integrity of mouse mammary glands, this study did not explore the possible impact of the changes caused by propyl paraben on the occurrence of breast cancer. Rodents exposed to parabens in infancy also experience altered mammary gland development. For instance, rats exposed to modest doses of methyl paraben during the perinatal, peripubertal, and pubertal periods showed altered mammary gland morphology and gene expression[188]. Human breast cancer gene signatures show an overrepresentation of genes impacted by methyl paraben[188]. According to a second study, adult mice exposed to propyl paraben for four days develop more R-loops[189], it has been connected to greater cellular stress and genetic instability as it builds up. This suggests that chromosomal instability caused by parabens may play a role in the development of breast cancer. Research has not yet convincingly demonstrated a link between exposure to parabens and the initiation or progression of breast cancer, particularly during significant exposure times. Overall, exposure to EDCs during critical times for breast cell proliferation and differentiation, such as adolescence and pregnancy, may have an impact on mammary gland development[190]. However, further research is required to fully understand this link.

In Vitro Evidence

There is currently a dearth of information about PFAS activity in in vitro breast cancer models. Human breast cancer cells are exposed to either PFOS or PFOA in vitro, which improves the effects of estrogen and increases cell growth and proliferation[191]. Breast epithelial cells (MCF-10A) exposed to PFOA are stimulated to migrate and invade through a PPAR-dependent mechanism, which raises the possibility that exposure may slow tumor growth by triggering neoplastic transformation[192].

In human breast cancer cells, parabens have been demonstrated to promote the characteristics of cancer[2]. Particularly, parabens promote breast cancer cell line growth at clinically meaningful levels[2,189]. In breast cancer cell lines, newly identified oxidized paraben metabolites can also promote proliferation in an estrogen receptor-dependent way[193]. In these investigations, the proliferative effects were seen after only a brief period of exposure, such as a few days. Parabens can cause breast cancer cells to migrate and invade more readily when given a longer course of treatment[194]. The effects of parabens on migration and invasion are estrogen receptor-dependent and more apparent after 20 weeks of therapy than after one week[194]. It has been suggested that parabens may be involved in the transformation of mammary epithelial cells since they have the ability to increase the proliferation of non-transformed human breast epithelial cells[195,196].

Although the focus of these investigations was on the effects of specific parabens, it is crucial to also take into account the possible consequences of paraben combination exposure. For instance, when paired with PFOA and bisphenol A (BPA), the effects of methyl paraben on cellular proliferation and apoptosis avoidance work in concert[197]. Additionally, non-cancerous human breast cells responded to combination therapy more favourably than cancerous ones[197]. More research is required to identify the precise processes underlying the effects of parabens on non-malignant and malignant breast cells, even though there is indication that these effects may be estrogen receptor mediated.

3.3.2.2 EDCs and Prostate Cancer

The prostate gland is one of the glands that are highly sensitive to EDCs effects since it is biologically controlled by hormones like androgens and estrogen[198]. Exposure to EDCs can lead to hormonal imbalance which in turn can be the cause for many prostate disorders including BPH (benign prostate hyperplasia) and PC (prostate cancer)[199]. Prostate cancer (PC) is one of the most common solid tumors affecting men with many risk factors for its occurrence[200]. Many EDCs have been linked to prostate cancer incidence including pesticides (highest effect), organophosphates, and cadmium[201]. Research from France, Canada, and other countries in the USA, as well as the American Agricultural Health Study has consistently linked occupational exposure to pesticides to prostate cancer[202-204]. An Australian analysis revealed no statistically significant correlations between self-reported occupational pesticide use and death, while only one study—from the Netherlands—identified a negative relationship between the two[205].

Other chemicals such phthalates, BPA, PBDEs, polycyclic aromatic hydrocarbons (PAHs), and PFAS yielded few results, and the findings for self-reported exposure to solely non-persistent pesticides were inconsistent. None of these studies were able to specifically evaluate the testicular dysgenesis syndrome hypothesis because they were all cross-sectional studies without information on prenatal exposure.

In Vivo Evidence

A previous study on the effect of bisphenol A (BPA) effect on prostate in mice found that the continuous exposure of low doses of BPA resulted in increased both Estrogen receptor 1 (Esr-1) and Androgen receptor (Ar) genes expression thus leading to permanent increase in prostate size and its hormone responsiveness[206]. Furthermore, rats administered neonatal low doses of BPA manifested prostatic intraepithelial neoplasia progression to carcinoma[207]. In general, prolonged adult exposure to EDCs can also trigger neo-plastic lesions and hyperplasia in addition to the unfavourable alterations in the prostate as study's findings indicated that long-term BPA exposure can promote immunological disruption, abnormal growth dysregulation and transcriptome reprogramming in adult rat prostate[208].

The exposure of a single maternal dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), which is the most potent and toxic type of dioxin, was found to be a possible cause of prostate carcinogenesis in rodents[209]. Moreover, polychlorinated biphenyls (PCB), organic pollutant, exposure also elevates the proliferation and metastasis of PC through the Aryl hydrocarbon receptor (AHR)[210]. AHR could increase androgen signalling pathway and thus carcinogenesis in prostate cancer cells[211]. Despite these evidences, the exact chemical mechanism by which dioxin and PCB increase carcinogenicity in prostate cancer is still unknown. Another EDC that affects prostate is di-(2-ethylhexyl) phthalate (DEHP) which is known for its alterations on the development and function of reproductive organs including the uterine and prostate[212,213]. DEHP exposure during pregnancy and lactation may disturb testosterone and estrogen balance and thereby increasing the risk of prostate cancer[214]. Estrogen hormone have also been linked to disturbance of prostate function and possibility of prostate cancer development[215]. Rats and mice exposed to prenatal doses of estrogen suffered from impaired prostate function, increased proliferation, inflammation, and dysplastic epithelial alterations later on[216].

In Vitro Evidence

Many in vitro studies focused on the effect of different EDCs on the prostate function and incidence of PC. For intense, an ecological study investigated the correlation between oral contraceptives use during pregnancy and the manifestation of prostate cancer in the child later on[217]. Prostate cancer incidence and mortality rates were correlated with the proportion of females who used contraceptives (oral and others). The results showed a significant relation between oral contraceptives use and prostate cancer ($p< 0.05$)[217]. furthermore, in another study, both benign and malignant human prostate cells were treated with 17-β- hydroxyestradiol for 72 hours either alone or in combination with leptin. The combination resulted in significantly higher growth in all cell types, while surprisingly, 17-β- hydroxyestradiol alone caused a reduction in cell growth in benign prostate hyperplasia cells[218]. The results align with other studies that shows either inhibition or increasing effect of estrogen on prostate cells[215,219,220].

Another EDC in relation with prostate cancer is phthalate. The presence of urinary phthalate metabolites was positively correlated with prostate carcinoma in obese men[221]. Phthalate carcinogenicity could be through its activation of peroxisome proliferator- activated receptor α (PPAR α) or by AhR receptor mentioned earlier[222]. Further studies are required in assessing the effect of each phthalate metabolite and their combination.

3.3.2.3 EDCs and Thyroid Cancer

Studies have linked EDCs to thyroid gland imbalance as they may affect thyroidal function in at different levels, the bioavailability of T3/T4 hormones, as well as central regulation processes at the hypothalamus or pituitary glands levels, all of which may interfere with the function of the thyroid gland[223,224]. There are numerous mechanisms in which thyroid-disrupting substances could cause a decreasing the levels of thyroidal hormones. These include: 1. iodide uptake inhibition, 2. thyroid peroxidase inhibition that induces disruption of thyroid hormone synthesis, and 3. increased uridine diphosphoglucoronosyl transferase enzymes[225]. According to several studies, exposure to certain EDCs alters thyroid function and is linked to a higher risk of a number of harmful health effects, such as thyroid diseases, developmental abnormalities, and several types of cancer[226-229]. Pesticides, polychlorinated biphenyls (PCBs), flame retardants, phthalates, perfluoroalkyl substances (PFAS), and bisphenol A (BPA) are EDCs linked to thyroid cancer[230]. Although they are known to be harmful to health and associated with thyroid cancer, they do not necessarily reduce thyroid hormone levels, and studies to date have been unable to determine their precise mechanism of action[231]. These chemicals can influence euthyroid state in a variety of ways, including "disturbance of thyroid hormone biosynthesis by directly targeting the sodium-iodide symporter (NIS)", "interaction with thyroid hormone transporters/receptors", "interference with the hypothalamic-pituitary-thyroid axis", and "disruption of multiple molecular alterations associated with thyroid pathogenesis"[232].

In Vivo Evidence

The most common endocrine system cancer in thyroid cancer with a faster incidence than any other malignancy[233]. Flame retardants are a widespread class of chemicals that is found in furniture, fabrics, plastics, and many other household products[234]. The similarity of flame retardants, such as decabromodiphenyl ether (decaBDE) and tris (2-chloroethyl) phosphate (TCEP), to natural thyroid hormones was found to cause disruption in the living organism thyroidal homeostasis and, most importantly, increased risk of thyroid cancer[235,236]. Despite the lack of in vivo studies on human, animal and in vitro studies prove the risk of EDCs interaction and alteration of thyroid function, specially in infants' later life when exposed during gestation. A study shows that shortly after the exposure to decabromodiphenyl ether during pregnancy and lactation in rats (146mg/kg/day) and mice (1500mg/kg/day), a significant drop in blood T3 levels were observed[237]. Another study showed negative effects of polybrominated diphenyl ethers on both adult rats and their developing offspring when they were exposed to it through gestation, and the highest concentration was found in breast milk proving lactational transfer of these chemicals to infants and new-borns[238]. In vivo studies have also included non-mammalian models[217,218]. For instance, a previous study studied the thyroidal disruption effect of phenanthrene, a polycyclic aromatic hydrocarbon found in pollution, on Arabian seabream fish[239]. Different phenanthrene concentrations were given to assess the changes in thyroid gland tissue, serum T3 and T4 levels, and the fish muscle content of phenanthrene. The results showed a significant impact of phenanthrene on thyroid function in fish as changes in T3 and T4 levels were observed along with a decreasing thyroid follicle epithelium and increased follicle diameter were shown[239].

In Vitro Evidence

Human studies have showed inconsistency regarding the exact effect of EDCs and flame retardants on thyroid hormones[240,241]. However, all studies showed strong correlation between increased levels of different EDCs and raised risk or incidence of thyroid cancer[242,243]. A case-control study regarding the effect of flame retardants (FRs),

specially decabromodiphenyl ether (decaBDE) and tris (2-chloroethyl) phosphate (TCEP), on the rates and severity of papillary thyroid cancer (PTC) showed that higher levels of FRs are associated with higher odds of PTC occurrence[235]. Another flame retardant, polybrominated biphenyl (PBB), was found to disrupt the thyroid function homeostasis through the suppression of thyroid receptor- mediated transcription in in vitro cell cultures[244].

Another study also studied PTC association with polybrominated diphenyl ethers and polybrominated biphenyls serum levels in US patients and proved the strong correlation between them[245]. The association was even higher in women and with larger thyroid tumor size (> 10mm)[246]. Furthermore, environmental pollutants bisphenol AF and phthalates presence in human serum was linked to an increased risk of developing thyroid cancer by 14 times[247]. Another study also linked the presence of 7 polycyclic aromatic hydrocarbon metabolites (organic pollutants) to manifestation of nodular goiter and PTC[243].

3.3.2.4 EDCs and Uterine cancer

EDCs are known to mimic natural hormones and negatively affect the function and growth of normal reproductive organs[116]. By exploiting epigenomic plasticity, intrauterine and early age exposure to EDCs may be the cause reprogramming of myometrial stem cells that results in mutations and possibility of cancer[248]. The EDC chemicals related to uterine disturbance and possibly cancer mainly acted on hormones, since uterine cancer is estrogen dependant [101]. Many different chemicals were included such as BPA, PFAS and EE.

EDCs, or substances that interfere with hormone activity, may be a modifiable risk factor for fibroid growth since estrogen and progesterone are crucial for fibroid growth and because reproductive-aged women are frequently exposed to EDCs[249-251]. Some EDCs, including diethylstilbestrol (DES), which may behave as estrogen agonists, have been implicated in the etiology of fibroid tumors, according to earlier research[252]. By mimicking endogenous hormones and inhibiting their binding to the receptors or interfering with their function and regulation, EDCs can change how hormones work by attaching to nuclear receptors[253]. Importantly, EDCs can have a non-monotonic dose response curve, meaning that even low concentrations of these chemicals might have pathologic consequences, especially when multiple chemicals are exposed simultaneously[37,254]. Certain EDCs have been linked to poor reproductive results in humans as well as reproductive toxicity in animal models[68,255-257]. The majority of in-vitro investigations show that EDCs, including DEHP and bisphenol A, boosted the proliferation of human fibroid cells, aiding in the development of fibroid[258-260]. A correlation between EDCs and pathways connected to inflammation is suggested by a number of fibroid mechanistic investigations[258,261]. In a study published in 2020 by Lee et al., fibroid prevalence among South Korean reproductive-aged women was compared to exposures to non-persistent EDCs. Transvaginal ultrasonography was used to detect the existence of fibroids. They discovered that frequent users of personal care items had higher associations between chemical exposures and fibroid risk, which included the usage of specific parabens and phthalates, such as ΣDEHP[262].

In Vivo Evidence

Several animal-model studies have been made in assessing the effect of EDCs on uterus and their role in progression of uterine cancer. BPA and 17 α- ethinyl estradiol (EE) are similar EDCs found in many ingested products such as food packaging and cans, as well as in oral contraceptives[263]. Another study examined the pathology of these two chemicals by exposing mice to continues oral doses of BPA and EE in a human exposure-mimicking doses[264]. Two different uterine diseases were found that were related to immunity and fibrotic pathologies, pyometra and equine endometriosis-like phenotype[264]. Both chemicals significantly increase uterine weight as they act in an estrogen-like action[265]. Moreover, rats exposed with low-dose BPA for a lifetime (25 and 250 μg/kg/day) showed pathology in oestrous cycle and uterine homeostasis[244]. The possible mechanism of action is proposed to be through the dysregulation of multiple estrogen receptors, but the exact mechanism is still unknown[100].

PCBs were also found to have a variety of mechanisms by which it is related to endometrial cancer incidence or progression[266]. One of the mechanisms that was found is by enhancing the inflammatory factors by estrogen and AHR receptors without altering normal estrogen levels[267]. To study the exact mechanism of dioxin products on AHR in living organisms, another study treated different strains of rats (dioxin-sensitive and -insensitive) with TCDD and examined the alterations in mRNA levels that are controlled by AHR[268]. Dioxin-sensitive rat strains exhibited higher transcriptional changes that could lead to endometrial disturbance and other adverse health problems[250,268].

In Vitro Evidence

Breast and uterine, gender-related, cancers are estrogen-dependent neoplasms. Epidemiologic studies linked several EDCs commonly used in personal care products like di-(2-ethylhxyl) phthalate (DEHP) and parabens to the increased risk of fibroids development and severity in female uterine[123]. BPA relation to uterine pathology is also widely studied as it is the most common estrogenic EDC present in numerous daily used plastic-products[269]. Higher BPA and PCB levels were associated with ovarian cancer and uterine cancer in female patients[133]. Furthermore, a small cohort study in Japanese women linked complex endometrial hyperplasia and cancer to low levels of serum BPA[270].

Polyfluorinated substances (PFAS) are another EDC, found in drinking water, that was shown to be associated with increased risk of uterine leiomyoma and PCOS in Swedish females[271]. Another study examined plasma levels of 7 PFAS in women with uterine fibroid and 9.4% fibroid prevalence rate was found. PFAS were not associated with fibroid number and initiation but rather affected fibroid growth enhancement or suppression (depending on the original fibroid volume)[272]. TCDD was investigated regarding its toxic effect on uterine in Seveso women[273]. In contrast to its estrogenic effect on breast, TCDD was showed to have an anti-estrogenic effect on the uterine myometrium and thus it is possible to have a different effect on mammary tissue and uterine endometrium, more studies are required regarding the mechanism for these observations[272,273].

CONCLUSION

Human studies have showed inconsistency regarding the exact effect of EDCs and flame retardants on thyroid hormones. EDCs are known to mimic natural hormones and negatively affect the function and growth of normal reproductive organs.

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