

Endocrine disrupting chemicals as potential risk factor for estrogen-dependent cancers

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ABSTRACT

Civilization, industrialization, and urbanization create an environment where humans are continuously exposed to endocrine disrupting chemicals (EDCs). Some of breast cancers and endometrial cancer, which are the most common female malignant neoplasms, are estrogen-dependent tumors. Prolonged exposure to estrogens or substances with estrogenic properties may be a risk factor for their development. This paper aimed to discuss the potential adverse effect of EDCs on human health, including the role of EDCs in hormone-dependent carcinogenesis. A review of literature regarding the sources of environmental exposure to EDCs and molecular mechanisms of their action was performed. We analyzed the possible mechanisms of how these substances alter the function of the endocrine system, resulting in adverse health effects. Hundreds of substances with endocrine disrupting potential have been identified in our environment. There is accumulating evidence linking exposure to EDCs with the development of mammary and endometrial cancer. By interacting with steroid receptors, EDCs can impact the cellular processes potentially leading to carcinogenesis. There are also data showing the effect of EDCs on immune dysfunction. During lifespan, people are usually exposed to a mixture of various EDCs, which complicates the assessment of individual substances or compounds implicated in cancer development. As the prevalence of hormone-dependent tumors among women continues to increase, their successful prevention is of human benefit. Institutions representing medicine, science, industry, and governments should develop joint strategies to decrease exposure to EDC, and thus to reduce the risk of hormone-dependent tumors in women.

Introduction Cancer is one of the major causes of death worldwide. Its prevalence increases every year and is expected to surpass that of cardiovascular diseases in the next few years.¹ Some of breast cancers as well as endometrial cancer, which are the most common female malignant neoplasms, are considered estrogen-dependent tumors. Estrogens play a key role in the development and function of the female reproductive tract. The prolonged exposure to estrogens, for example, through early menarche, late menopause, or the use of hormone replacement therapy, is a known risk factor for these tumors. A positive correlation between high levels of circulating estrogens with breast and endometrial cancers was found.^{2,3} The other risk factors for these neoplasms are those associated with modern lifestyle such as sedentary life, which leads to obesity, as well as late first pregnancy.⁴

Carcinogenesis depends on a variety of different mechanisms and factors, both genetic and environmental (chemicals, radiation, viruses).⁵ Chemical factors include well-known carcinogens such as benzene, asbestos, or formaldehyde. The role of endocrine disrupting chemicals (EDCs) in carcinogenesis has not yet been fully explored. EDCs influence hormonal profile interactions, and therefore may lead to hormone-dependent carcinogenesis. The timing of exposure to environmental factors is essential to the development of cancer.

The aim of this review was to present the potential adverse health effects of exposure to EDCs, and the role of avoiding exposure to these chemicals in the prevention of breast and endometrial cancers.

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Endocrine disrupting chemicals Civilization, industrialization, and urbanization alter the world in a way that continuously exposes humans to significant doses and variety of chemicals. Air, water, and food contamination as well as unhealthy lifestyle, involving tobacco smoking and bad dietary habits, increase the prevalence of cancer. The chemicals could act as carcinogens that directly or indirectly cause genomic damage, genome instability, or epigenetic modifications and impair cellular regulatory processes involved in apoptosis.⁶ Thus, these substances may influence cancer development and progression, as well as the effectiveness of treatment.

According to the definition proposed by the World Health Organization (WHO), EDCs are exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub)populations.⁷ Close to 800 chemicals are known or suspected to have the endocrine disrupting potential.⁸ Among them, bisphenol A (BPA), esters of the phthalic acid (phthalates, PAE), hexachlorobenzene (HCB), polychlorinated biphenyls (PCBs), dichlorodiphenyltrichloroethane (DDT) and its metabolites, as well as parabens are suspected to be involved in the pathogenesis of hormone-dependent cancers.⁹ These substances, due to their phenolic structures, can interact with estrogen, androgen, and progesterone receptors.

Exposure to endocrine disrupting chemicals People are exposed to a number of known and unknown EDCs with different properties and mechanisms of action. Such exposure occurs directly and indirectly, in different concentrations and timing, including in utero exposure. The pervasive presence of EDCs means the ongoing exposure of fetuses, neonates, children, teenagers, and adults to the mixtures of chemicals. The persistence of EDCs in the environment, as well as their toxicity and bioaccumulation in various organisms (even at very low concentrations) may have negative impact on human health.

BPA and PAE are commonly used as plasticizers in food packaging, bottles, electronic equipment, cosmetics, medical devices, and children's toys. They are also present in enteric coatings of pharmaceutical pills, printing inks, textiles, dental sealing, carbonless receipts, eye lenses, and water pipes.¹⁰ PCBs are used in industrial chemistry for the production of electronic transformers, capacitors, and cooling fluids. Food is the major source of human exposure to EDCs. Contamination with BPA and PAE can be caused by the migration to food stored in polycarbonate plastics or cans coated with epoxy resins. The temperature and time of heating as well as food composition play a key role in BPA and PAE releasing from food storage. The oral exposure is enhanced by consuming fresh food containing phytoestrogens or contaminated with organochlorines (ie, PCB). The other ways of exposure to EDCs

include inhalation (home dust) or transdermal route (thermal paper, cosmetics).

Estrogen receptors: the key modulators of the action of endocrine disrupting chemicals The main estrogens: 17 β -estradiol and estrone act on target tissues via 2 subtypes of estrogen receptors (ERs), ER α and ER β ,¹¹ which are ligand-dependent transcription factors and interact with DNA sequences called estrogen-responsive elements. These receptors vary in tissue distribution and transcriptional activities.¹² In animal studies, ER α can mediate the estrogen-induced proliferation, whereas ER β repress the proliferation and promote apoptosis.¹³ There are two ways of estrogen signaling. The classic pathway, called "genomic", is mediated by ERs located in the nucleus. It modulates the expression of selected genes, thus influencing the selected mRNA and protein levels.¹⁴ The second, nongenomic pathway involves the membrane-bound ERs. This pathway is more rapid and is based on cellular signal transductions via calcium ions, nitric oxide,¹⁵ tyrosine kinases, mitogen-activated protein kinases (MAPK),¹⁶ adenylyl cyclase,¹⁷ as well as phospholipase C.¹⁸ Target cells are able to modulate the response to estrogens via a variety of mechanisms: inhibition of ER expression by ER gene transcription blockage,¹⁹ ER proteolysis,²⁰ and epigenetic methylation of the ER α gene.²¹

EDCs potentially interfere with estrogen-dependent cell signaling (genomic and nongenomic pathways), leading to carcinogenesis in different ways. For example, EDCs can alter the activity of enzymes involved in estrogen steroidogenesis, resulting in increased serum estrogen concentrations.²² These results were reported both for benign and malignant neoplasms of the female reproductive system.

Effect of endocrine disrupting chemicals on estrogen-dependent processes that may be involved in carcinogenesis

The growth and proliferation of estrogen-dependent tumor cells require the presence of ER; thus, many of cancer cells are characterized by the upregulation of ER α and/or ER β .²³ The clinical effects of the modulatory impact of exogenous ER-ligands was shown, among others, for tamoxifen and its derivatives (raloxifen, toremifen), nowadays called selective estrogen receptor modulators, which show antagonistic effects in breast cancer cells and agonistic—in endometrial cancer cells.²⁴ As EDCs can interact with ERs, these chemicals can influence cell cycle and proliferation. EDCs, such as PAE and brominated flame retardants, may lead to cyclin D1 upregulation and p21 protein downregulation (proteins involved in the cell cycle regulation).²⁵ PAE was found to influence the expression of cdk-4 and lymphoid enhancer-binding factor 1 that may be associated with disease progression.²⁶ EDCs may act also on cell cycle via other molecular pathways such as activation of protein kinase C, phosphatidylinositol 3-kinase, MAPK,²⁷ or p53 pathway.²⁸

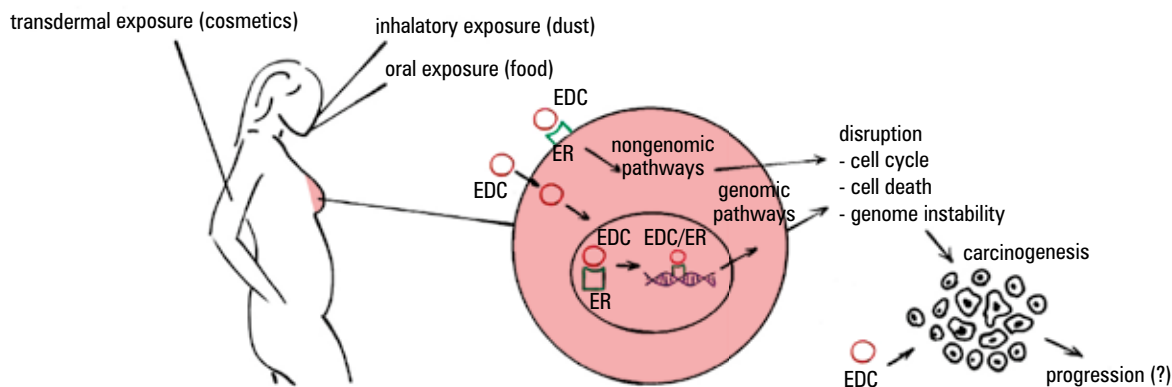


FIGURE 1 Possible mechanisms of the effect of endocrine disrupting chemicals on carcinogenesis
Abbreviations: EDC, endocrine disrupting chemical; ER, estrogen receptor

The type of response and effects depend on a variety of factors including the type of EDC, the target tissue, ER expression, and the ER α /ER β ratio, as well as the presence of different cofactors.

Genome instability, defined as an increased tendency of a genome to acquire mutations, is one of the main mechanisms leading to cancer development.²⁹ It is a result of impairment of DNA repair, DNA damage response, instability of telomeres and disruption of their length, and epigenetic modifications (DNA methylation, histone modifications). Available evidence confirms that low-dose exposure to EDCs impacts genome instability. The most common plasticizers such as BPA and PAE were shown to increase the epigenetic modifications such as changes in DNA methylation or histone modification.³⁰ BPA was shown to act on the formation of micronuclei, impairing the cell cycle³¹ and DNA damage response.³² It may also disrupt the double-strand repair machinery leading to DNA instability.³³

Exposure to endocrine disrupting chemicals and the risk of breast cancer

Breast cancer, the most common cancer in women, is increasing in prevalence worldwide. In 2012, it was diagnosed among 1.67 million women. In comparison, according to the WHO data, in 2008, there were 1.38 million cases. By 2020, the number of women with breast cancer is expected to reach 1.98 million.

Genetic factors, prolonged exposure to estrogens, obesity, high socioeconomic status, and poor food quality are the proven risk factors for breast cancer development.³⁴ The risk of breast cancer in adults depends on hormonal milieu during pre- and perinatal life.³⁵ EDCs that mimic the action of estrogens may affect carcinogenesis in the mammary gland with different intensity according to the type, dose,³⁶ and the timing of exposure.³⁷ Animal studies have shown that throughout the life span EDCs may increase the risk of breast cancer progression through different mechanisms. These involve modifications of the fetal mammary gland development (without

morphological changes) that increase the carcinogenic sensitivity, or demonstrate tumor cell growth through estrogenic signaling.³⁸

Currently, 216 chemicals are suspected to increase the risk of mammary cancer.³⁹ Additionally, more than 100 EDC-related chemicals are widespread mammary carcinogens,⁴⁰ and approximately 60 lead directly to tumorigenesis in this tissue.⁴¹ Numerous EDCs, including atrazine, diethylstilbestrol (DES), dibutylphthalate, polybrominated diphenyl ethers, and nonylphenol, were described to interfere with the development of the mammary gland.⁴² These substances may alter the growth of this gland, influence gene and protein expression, and cause changes in the numbers of terminal ducts and in histological structure of the breast tissue.⁴³ A positive correlation between breast cancer development and serum concentrations of selected chemicals has been reported.⁴⁴ The possible mechanisms of the effect of EDCs on carcinogenesis are summarized in **FIGURE 1**.

In utero exposure to endocrine disrupting chemicals and the risk of breast cancer

Estrogens, among other hormones and growth factors, such as prolactin, oxytocin, insulin, insulin-like growth factor, growth hormone, thyroxin, and progesterone, play the pivotal role in breast tissue development.⁴¹ Prolonged exposure to EDCs may affect the process of mammary gland development by mimicking estrogenic action⁴⁵ and influence the prenatal formation of the breast tissue.^{41,46} The transfer of EDCs from the mother to fetus via placenta, and to newborn offspring through breast milk has been well described.⁴⁷ Some data confirm high-specificity and binding affinity of the EDCs to estrogen-related receptors gamma, which are highly expressed in the placenta, developing fetus, and neonate.⁴⁸ BPA, PAE, and their metabolites were detected in the amniotic fluid,⁴⁹ human placenta,⁵⁰ umbilical cord blood,⁵¹ and breast milk.⁵² Thus, they may significantly impact the fetal and neonatal development. It has been

postulated that perinatal exposure may be more important to the development of breast tumor than adult exposure.⁵³ BPA may influence the fetal stroma, which expresses the ER and thus may alter developmental processes in breast tissue.⁵⁴ It may disrupt adipocyte differentiation in the fat pad and periductal stroma through activating the ER signaling in the mesenchyme, thus altering proper ductal development.³⁵ Rats exposed to low dose of BPA (2.5–25 µg/kg body weight) in utero showed increased cell proliferation and proliferation/apoptosis ratio in the mammary gland compartments.⁵⁵ Exposure to BPA during prenatal life has also been shown to accelerate and modify the alveolar buds.⁵²

Of note, this time of exposure may lead to epigenetic changes in fetal DNA.^{30,56} Animal models have shown that exposure to EDCs of a pregnant woman has resulted in epigenetic modifications and biological effects present up to the third generation.⁵⁷

Pubertal and adult exposure to endocrine disrupting chemicals and the risk of breast cancer

Puberty is the time of the intensive development of the terminal endbuds of the mammary gland, the most undifferentiated epithelial structures with high sensitivity to carcinogens.⁵⁸ Thus, this stage of life may be very susceptible to the disrupting potential of EDCs. The risk of progression to breast cancer is associated with an increase in the number of terminal endbuds.⁵⁹ The positive correlation between exposure to different BPA concentrations and changes in these structures was confirmed in animal studies.⁶⁰ Oral exposure to higher doses of BPA (5 µg – 5 mg/l of drinking water corresponding to 0.6 µg to 1.2 mg/kg body weight) resulted in alterations in the number of terminal endbuds. Likewise, after exposure to DES, perinatal exposure to BPA increases epithelial cell numbers in the mammary gland in adulthood.⁶¹

The risk of breast cancer increases as women get older. At this stage of life, there are many estrogen-dependent risk factors such as the use of oral contraceptives and hormone-replacement therapy, in addition to widespread exposure to environmental EDCs. Occupational exposure to EDCs was described in groups of cashiers exposed to BPA from thermal paper,⁶² women employed in food canning or automotive plastics,⁶³ and the manufactures of nonmetallic mineral products and chemicals.⁶⁴ These occupations are linked to higher exposure to EDCs and plasticizers and to higher risk of breast cancer, suggesting the potential role of these chemicals in breast carcinogenesis.

The adult exposure to BPA may play a role in initiating the growth of estrogen-dependent tumors.⁵² Animal studies support the data about the ability of BPA to induce premalignant or malignant lesions⁶⁵ and carcinoma in situ.⁶⁶ The exposure to BPA has increased also the expression of enhancer of zeste homolog 2, a factor thought to inhibit genes responsible for suppressing

tumor development and thus enhancing cancer progression.⁶⁷

BPA as well as other EDCs may act via many more pathways that may lead to increased risk for carcinogenesis, than described in this paper. Many of such molecular actions seem to be non-classic and independent of ER. EDCs may also act as obesogens, promoting obesity and thus indirectly facilitating cancer development.⁶⁸

Epidemiological studies of exposure to endocrine disrupting chemicals and the risk of breast cancer

Studies of exposure to various EDCs and the risk of breast cancer development in humans are still limited. A positive correlation between serum concentrations of monoethyl phthalate (MEP), early menarche, and breast development was found. Thus, perinatal exposure to phthalates may impact the concentrations of sex hormones during puberty and the timing of sexual maturation.⁶⁹

High serum MEP and BPA concentrations correlated with higher breast tissue density. However, no association between other EDCs concentrations (including monobutyl phthalate, butyl paraben, nonylphenol, and octylphenol) with this parameter was found.⁷⁰ A positive correlation, stronger in premenopausal women, was reported between urinary concentrations of mono (2-ethyl-5-oxohexyl) phthalate and breast cancer prevalence. Moreover, fat tissue and serum concentrations of several organochlorines, including PCB, have also shown a positive correlation with breast cancer development.⁷¹

In vitro and animal studies on the role of endocrine disrupting chemicals in the pathogenesis of breast cancer

In vitro studies evaluating the role of EDCs in breast cancer typically consider the relationship between exposure to a single EDC and specific cellular response. Despite such limitation, this method of modeling is useful in predicting biological effects of EDCs.

Estradiol and low dose of BPA administered in vitro enhanced the proliferation of human mammary endothelial cells.⁷² Triclosan and octylphenol were described to influence cell proliferation by altering the expression of cyclin D1 and p21, and G1/S phases transition of the cell cycle.⁷³ BPA exposure leads to increased oxidative stress and cellular proliferation.⁷⁴ MCF-7 cells exposed to low doses of BPA resulted also in intracellular Ca²⁺ increase,⁷⁵ which may affect cell proliferation and migration, leading to cancer progression.⁷⁶ It was also reported that chemoresistance in both ER α -positive and ER α -negative breast cancer cells might be linked with the exposure to low doses of BPA.⁷⁷ As slow-dividing progenitor cells are more vulnerable to the environmental factors and epigenetic mechanisms,⁷⁸ some studies confirming this theory have been conducted. It seems that benzyl butyl phthalate may contribute to breast cancer development via demethylation of ER promoter-associated CpG islands.⁷⁹ EDCs may also

trigger epigenetic modification leading to silencing of the p53-ARF apoptotic pathway in different breast cancer cell lines.⁸⁰ There are also data confirming the effect of EDCs on nonprotein coding RNA, which are differentially expressed in various cancers, including breast cancer.⁸¹ BPA induces the activation of signal transduction pathways, which mediate migration, AP-1/NFκB-DNA binding activity, and the invasion process in breast cancer cells.⁸² The similar observations were found for the human breast epithelial cells, MCF-10A, exposed *in vitro* to low doses of BPA, which induces molecular changes in protein phosphorylation. The increase of the *c-Myc* proto-oncogene, which has a pivotal role in growth control, differentiation, and apoptosis, leads to its abnormal expression characteristic of many tumors.⁸³

In utero exposure to BPA resulted in significant changes to inflammatory modulators within mouse mammary tissue.⁸⁴ This suggested that dysregulation of an immunoregulatory cytokine (both proinflammatory and anti-inflammatory) with subsequent immune dysfunction could lead to a cellular microenvironment that promotes breast cancer development. The immune system plays a key role in preventing cancer because it is capable of detecting and destroying transformed cells.

Exposure to endocrine disrupting chemicals and endometrial cancer Endometrial cancer is the most common gynecologic cancer that affects postmenopausal women at an average age of 60 years at diagnosis.⁸⁵ The risk factors for the endometrioid type are similar to those for other hormone-dependent tumors, such as breast cancer. Therefore, prolonged exposure to EDCs with estrogenic properties could cause the development of this tumor. The studies on the role of EDCs in endometrial cancer are much more limited compared to those involving breast cancer.

***In vitro* and animal models for evaluation of exposure to endocrine disrupting chemicals and the risk of endometrial cancer** *In vitro* studies have confirmed the estrogenic potential of BPA in human endometrial cells.⁸⁶ EDCs have influenced human endometrial endothelial cell proliferation and the viability of these cells *in vitro*.⁸⁷ Notably, *in vitro* treatment with DEHP leads to increased viability of endometrial stromal cells.⁸⁸ BPA also influences endometrial angiogenesis *in vitro*.⁸⁹ BPA could promote migration and invasion ability of human endometrial carcinoma cells by inducing cyclooxygenase 2 (COX-2) gene expression through the mechanisms involving the MAPK pathway and epithelial-to-mesenchymal transition (EMT), a process in which epithelial cells lose their cell-cell junctions and acquire the mesenchymal phenotype.⁹⁰ The elevated COX-2 level could promote cancer progression by inducing various effects such as invasion, angiogenesis, suppression of host immunity, resistance to apoptosis, and EMT. Numerous studies indicated that EMT

plays a key role in tumor progression, metastasis, and recurrence.

Animal studies have shown that neonatal exposure to BPA has resulted in severe pathologies of the uterus including atypical hyperplasia.⁹¹ Similar results were observed after neonatal treatment of mice with DES and genistein, which led to the development of uterine adenocarcinoma.⁹² The influence of BPA on uterine progress and pathophysiology were described by Suvorov et al.⁹³ Postnatal BPA exposure affects the steroid hormone-responsiveness of the uterine stroma,⁹⁴ and may influence the expression of morphoregulator genes such as *Hox* genes involved in uterine development.⁹⁵ *In utero* exposure of rats to BPA promotes uterine disruption in offspring, which is connected with dysregulation of ER. Administration of DEHP may lead to compromised endometrial receptivity.⁹⁶ Moreover, DEHP was described to disrupt the MAPK and NF-κB signaling pathways,⁹⁷ which are crucial molecular pathways in cellular signaling.

Epidemiologic studies of exposure to endocrine disrupting chemicals and endometrial cancer Increased levels of dichlorodiphenyldichloroethylene (DDE, the metabolite of DDT), HCB, and some congeners of PCB were detected in abdominal adipose tissue of patients with endometrial stromal sarcoma, which supports the thesis of their tendency towards bioaccumulation in human tissues and may probably facilitate their negative impact on cells.⁹⁸ There were also other data suggesting the possible role of DDE in endometrial cancer.⁹⁹ No increased risk for endometrial cancer after organochlorine exposure was reported.¹⁰⁰ However, further studies are needed to find more correlations between exposure to EDC and the risk of this cancer.

Conclusions The prevalence of breast and endometrial cancers increases dramatically every year, thus their prevention is of human benefit. Hundreds of substances with endocrine disrupting potential have been identified in our environment, as well as in human biological fluids and tissues. BPA has gained much attention because of its ubiquitous presence in the environment. Despite accumulated evidence linking EDCs exposure to mammary and endometrial carcinogenesis, the mechanisms by which EDCs affect the development of these tissues and increase cancer risk as well as cancer progression are unknown. Results from animal research may not be directly applicable to humans. Owing to chemical structures of EDCs, they interact with steroid receptors and could impact the cellular processes leading to potential carcinogenesis by genomic and nongenomic molecular pathways across the life course. Immune dysfunction that leads to a cellular microenvironment that promotes cancer development is another postulated mechanism. Mothers exposed to EDCs transfer them via the placenta to the fetus and increase the risk of epigenetic

DNA changes in offspring, promoting the higher risk for cancer development long after cessation of exposure. Such effect could influence up to 3 generations. The number of man-made EDCs is still growing as industrialization advances. Thus, the exposure to them of fetuses, neonates, children, and adults is dramatically increased and prolonged. Environmental exposure to these chemicals typically occur in combination, thereby complicating the ability to identify whether one or more substances are implicated in cancer development and cancer risk in women, including breast and endometrial cancers. It is of human benefit to avoid exposure to EDCs. Higher consciousness and better protection of pregnant and lactating women as well as young children is crucial to avoid the adverse health effects in the next generations. The increased precaution to reduce the EDC exposure among these vulnerable groups may be the key aspect in the prevention of estrogen-related cancers. Institutions representing medicine, science, industry, and governments should develop joint strategies to reduce the exposure to EDCs and to increase cancer prevention. Additionally, informing women on how to avoid EDCs in daily life may bring positive effects.

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Związki endokrynnie czynne jako potencjalny czynnik ryzyka nowotworów estrogenozależnych

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SŁOWA KLUCZOWE

karcynogeneza,
rak endometrium,
rak piersi, związki
endokrynnie czynne

STRESZCZENIE

Postęp cywilizacyjny, industrializacja i urbanizacja tworzą środowisko, w którym ludzie stale narażeni są na związki endokrynnie czynne (*endocrine disrupting chemicals* – EDC). Część raków gruczołu piersiowego i endometrium, stanowiące jedne z najczęstszych nowotworów złośliwych u kobiet, są guzami estrogenozależnymi. Przedłużona ekspozycja na estrogeny lub substancje o działaniu estrogenym mogą być czynnikiem ryzyka rozwoju tych nowotworów. Celem pracy było omówienie potencjalnego negatywnego wpływu EDC na zdrowie człowieka, w tym roli tych substancji w procesie hormonozależnej karcynogenezy. Dokonano przeglądu piśmiennictwa dotyczącego źródeł środowiskowego narażenia na EDC oraz molekularnych mechanizmów działania EDC. Przeanalizowano potencjalne mechanizmy dotyczące sposobu, w ramach których substancje te wpływają na czynność układu dokrewnego, w konsekwencji wywołując negatywne skutki zdrowotne. W środowisku człowieka wykryto setki substancji o właściwościach endokrynnych. Pojawia się coraz więcej dowodów istnienia korelacji między ekspozycją na EDC a rozwojem raka piersi i raka endometrium. Poprzez interakcje z receptorami steroidowymi EDC mogą wpływać na procesy komórkowe potencjalnie prowadzące do karcynogenezy. Istnieją również dane wskazujące na występowanie zaburzeń immunologicznych pod wpływem EDC. Człowiek, w czasie swojego życia, narażony jest zwykle na mieszaninę różnych EDC, co utrudnia ocenę wpływu poszczególnych substancji czy związków na ryzyko rozwoju nowotworu. Częstość występowania u kobiet nowotworów hormonozależnych stale wzrasta, dlatego ich skuteczna prewencja jest niezwykle istotna dla ludzkości. Instytucje reprezentujące medycynę, naukę, przemysł oraz władze powinny stworzyć wspólną strategię działania w celu ograniczenia narażenia na EDC, a w konsekwencji zmniejszenia ryzyka występowania hormonozależnych nowotworów u kobiet.

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