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Commentary

Impact of endocrine disrupting chemicals (EDCs) on the predisposition of cancer and polycystic ovary syndrome (PCOS): A Note

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Abstract

Endocrine Disrupting Chemicals (EDCs) or Endocrine Disruptors are unique assemblage or cluster of emerging pollutants as they affect the synthesis, release and transport of hormones. EDCs have been associated with a diverse array of health issues and diseases. EDCs can alter the endocrine system and are involved in carcinogenesis and inducing poly-cystic ovary syndrome (PCOS). The objective of this article is to furnish an outline of research on environmental aspects of EDCs and their effects on human health specially on cancer and PCOS based on evidence from animal and human studies. EDCs include natural compounds such as phytoestrogens and various synthetic chemicals which are utilized by the chemical, agriculture, cosmetic and food industries. Several EDCs may work as carcinogens and causes initiation and advancement of cancer. Uterine and ovarian cancers of female have been associated with exposure to EDC. Bisphenol-A (BPA), an EDC which is found in plastic bottles, household materials, canned food, waste water, beverage containers and thermal paper, can increase risk of breast cancer. Even low levels of BPA exposure may poses threat of prostate cancer in men. Testicular cancer and thyroid cancer could be influenced by EDCs. Comprehensive studies have been conducted by many researchers in the light of toxicity pattern of EDC that render interpretation of impact of EDCs on development of cancer and PCOS inducing capacity in female reproductive system.

Keywords: Endocrine disrupting chemicals; EDC; Cancer; Endocrine Disruptor, Poly-Cystic Ovary Syndrome; PCOS

COMMENTARY/NOTE

Endocrine Disrupting chemicals (EDCs) are described by the Endocrine Society as "an exogenous (non-natural) chemical, or a mixture of chemicals, that interferes with any aspect of hormone action." [1] The diverse galaxies of endocrine disrupting chemicals have been found.[2] EDCs may amplify through the action of biological and physicochemical transformation processes and eventually showing ability to produce cascades of other modified structures as per instance metabolites. Interestingly, some metabolites gain their own biological activities. The function of endocrine system has been altered by the action of EDCs.[1] By mimicking the hormones, EDCs bind with different receptors and attenuate normal functions of hormones thereby interfering endocrine homeostasis.[3, 4] In 2009, some highlighted works on the adverse effects of EDCs opened more avenues of research on EDCs.[5] Studies show that emerging contaminants are the newer alarming threat to ecosystems as well as human health.[6] Carcinogenesis is caused by DNA damage which is related to several exogenous and endogenous agents [7, 8] of which EDCs possess carcinogenic properties.[9] Experiment conducted in rodents shows that fetal as well as pre-pubertal exposure to EDCs influence the development of breast and uterine cancer.[10]

Bisphenol-A (BPA) is a common EDC in present-day of the contemporary world. Interaction between EDCs and human endocrine system in relation to various hormone-related diseases has been reported.[3] The effect of BPA as carcinogen on the reproductive system of women has been reviewed by Dumitrascu et al. [11] It has been observed that BPA has potentiality to interact with estrogen receptors (ERs) and thereby take part in estrogen signaling pathways.[12] Epigenetic modifications and the molecular mechanisms of BPA action in various types of cancers have been well documented.[13] Role of BPA on urological cancers (prostate and bladder cancer) has been reviewed by Pellerin et al[14] Polychlorinated biphenyls (PCBs) and phthalates which are EDCs may be linked to an enhanced threat of cancer in thyroid gland.[15] (Table 1)

EDCs have been reported to be involved in the progression of breast and uterine cancer and public awareness about exposure to EDC reduces the threat of female cancer.[16] It has been emphasized that EDCs may play important role on starting and progression of reproductive problems and cancers associated with endocrine glands in female.[17] It has been observed that PCOS –like symptoms have been induced by BPA. [18, 19] BPA is linked to abnormalities of female endocrine system and complications of the female reproductive system. [20-24] Interference of BPA has been observed on steroidogenesis in ovarian granulosa cells of

women.[25] It has been reported earlier that in female with PCOS, the level of serum BPA was high.[26] Exposure to BPA has been linked to female with PCOS.[27] Evidence showed that BPA might have a role in the pathogenesis of PCOS.[28,29] (Table 1)

Pivotal role is played by BPA in the development of female reproductive and metabolic disorders such as PCOS and hyper-androgenism as well as insulin resistance obesity [18,19,30,31] Exposure of BPA (50 µg/kg bw/d) in adult female Sprague-Dawley rats showed estrous cycle disorder, enhanced serum testosterone level and polycystic ovary.[32] BPA analogues induce a process that causes fertility related complications and PCOS.[33-36] Experimental results indicated that exposure to BPA is linked to diagnosis of PCOS and serum concentration of BPS (bisphenol S, analogue of BPA) in serum is high in women with PCOS.[37]

It has been observed by substantial evidence from experiments in mice and rats that they are susceptible to mammary gland cancer following BPA exposures below the oral reference dose (RfD)[38,39] It has been revealed that elevation of urinary BPA levels is associated with prostate cancer in humans.[40] Review has been done on environmental chemicals where Zebra fish (*Danio rerio*) is used as a model animal for the toxicological study to show the effects of these chemicals as endocrine disruptors.[41] Cosmetic products which are considered as emerging pollutants having potential of persistence and bioaccumulation ability can cause a risk to ecosystem and human health.[42] The fetal prostate development is affected by exposure to estrogens and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD).[43,44]It has been reported that some detrimental consequences of EDC exposure are obesity, altered behaviors and infertility.[45]

Insulin resistance eventually causes hyperinsulinemia hyper-tension and type 2 diabetes mellitus.[46,47] PCOS possesses threat to women having a greater threat of heart related diseases which is the primary reason of female demise globally.[48] It has been shown that women with PCOS having high BPA level gave rise to visceral typed obesity, dyslipidemia, hyperinsulinemia as well as insulin resistance and increased androgen level.[49] Women diagnosed with PCOS have been showed manifestation of hyperandrogenism, chronic oligo/anovulation, and/or morphology of polycystic ovary which ultimately leads to infertility.[50] As the PCOS is linked to obesity,[51] females who are obese and diagnosed with PCOS, are generally showing Insulin Resistance (IR) which in turn involves in pathogenesis of PCOS.[52] Metabolic and reproductive problems related to PCOS aggravate and deteriorate due to mainly visceral obesity.[53] Plasticizers such as phthalates and bisphenols take part in occurrence and progression of PCOS.[54] It has been reported that the exposure to EDC posing a threat of reproductive dysfunction.[55-57], cognitive shortage[58-60], metabolic disorders[61,62] and also development of cancers[63-65]. Lee et al.[66] reported that estrogen receptors (ERα and ERβ) are activated by EDC during developmental period not only enhance the risk of infertility in both sexes but also increase incidence of reproductive tract cancer in women and prostate cancer in men. It is reported that EDCs such as Diethylstilbestrol, dichlorodiphenyl trichloroethane, dioxins and bisphenol-A have potentiality to increase risk of breast cancer.[67]

It has been reviewed that EDCs play a role in the generation of comorbid disease and disruption of the immune system.[68] Estrogen receptors could be induced by some EDCs like BPA, di(2-ethylhexyl)phthalate (DEHP) and dioxins causing prostate and breast cancers which are estrogen-dependent.[69] Exposure to EDC may have been linked with male genitourinary cancers.[70] Impairment of endocrine system of human has been observed after exposure to EDC resulting in heart related, metabolic, and immune system dysfunctions in human beings.[71] (Table 1) After attaching with estrogen receptors EDCs cause activation of protein-1 (AP-1), nuclear factor-kappa B (NF-κB), and specificity factor-1 (Sp1) which are acted as transcription factors, thereby inducing many chronic and comorbid diseases.[71-73]

It has been suggested that establishment of International Agency for Research on EDCs and comprehensive testing strategies are needed for identification of EDCs and as well as implementations policies relating to effect of EDCs.[74] Kahn et al.,[75] have extensively studied on EDC exposure and their effects on human health which has been published in The Lancet Diabetes & Endocrinology. This work will open many avenues which will help to understand how human health adversely affected by EDCs.

It is a humble attempt towards focusing attention on some recent developments in this field of research and efforts have been made for projecting this scientific understanding to a wider array of modern researchers who can take the torch forward to resolve some still unresolved issues of toxicology in relation to endocrine disruption mediated human health problems including cancer and polycystic ovary syndrome (PCOS). Public awareness programs on the possible exposure of EDCs and their adverse effects need to be propagated by the Government among the naïve human population who are unknowingly and silently assaulted by EDCs, so that the disease incidence owing to its exposure will be minimized in near future. Based on existing researches and available literatures on Endocrine Disrupting Chemicals it has been observed that EDCs especially BPA can induce cancer and show strong possibility of development of PCOS associated with reproductive complications, insulin resistance, type 2 diabetes and hyperandrogenism in female. Studies have explored the effects of EDC exposure on features of polycystic ovary syndrome (PCOS) and it is evident that premenopausal women exposed to EDC, disrupt the normal function of female reproductive system leading to PCOS. EDCs especially BPA becomes a risk factor to human health and reproduction. PCOS induces several problems which endangering reproductive system of woman and disrupting ovarian steroidogenesis causing enhanced possibilities of infertility.

Table 1: EDC compounds and their pathological association especially related to cancer and PCOS.

EDC Compound	Action/Effect	References
Bisphenol A (BPA) & Dioxin	Carcinogenic	[9]
Polychlorinated biphenyls (PCBs) & parabens	Enhances breast cancer risk	[10], [16], [17]
BPA	Enhances breast cancer risk	[16, 38, 39]
	Carcinogenic for reproductive organs of women	[11]
	Modulate estrogen signaling by interacting with estrogen receptors (ERs)	[12]
	Causes epigenetic modifications in different cancers	[13]
	Induce prostate and bladder cancer	[14, 40]
	Associates with ovarian and endometrial cancer risk	[17]
	Associated with fertility related complications and induction/pathogenesis of poly-cystic ovarian syndrome (PCOS)	[18, 19, 27,28, 33-36, 37]
	Related to female endocrine disruption and reproductive complications	[20-24]
	Interferes steroidogenesis in ovarian granulosa cells	[25]
	Female reproductive and metabolic disorders such as PCOS, hyper-androgenism, insulin resistance, and obesity	[18, 19, 30, 31]
PCBs, Phthalates, BPA, Polyfluoroalkyl Substances (PFAS), Agricultural Pesticides (Organochlorine, Organophosphate, alachlor and triazine)	Enhance the risk of thyroid gland cancer	[15]
Mono-(2-ethylhexyl) phthalate (MEHP), organochlorine pesticides, diethylstilbestrol (DES), benzyl butyl phthalate (BBP), 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), BPA, parabens, dichloro-diphenyl-trichloro-ethane, dioxins	Associates with breast cancer risk	[17, 65, 67]
di-*n*-butyl phthalate (DnBP),	Associates with ovarian cancer risk	[17]
Phthalates, BPA, parabens	Affect sperm motility, concentration, spermatogenesis and steroidogenesis. Associated with PCOS and impaired fertility.	[65]
BPA, Nonyl-phenol (NP) and octyl-phenol (OP), DES, PCB, di(2-ethylhexyl) phthalate (DEHP), dioxins, phthalates	Activate estrogen receptors (ERα and ERβ), enhance the risk of infertility, increase incidence of ovarian, endometrial, estrogen dependent breast cancer and prostate cancer, diabetes, obesity	[66, 69, 71]

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