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Possible relationship between endocrine disrupting chemicals and hormone dependent gynecologic cancers

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ABSTRACT

The effects of the natural and synthetic estrogens have been studied for a long time but the data regarding estrogen related chemicals (endocrine disrupting chemicals, EDCs) and their effects on reproductive system are scarce. EDCs are hormone like agents that are readily present in the environment, which may alter the endocrine system of humans and animals. Approximately 800 chemicals are known or suspected to have the potential to function as EDC. Potential role of EDCs on reproductive disease has gained attention in medical literature in recent years. We hypothesize that exposure to low doses of EDCs in a chronic manner could cause hormone dependent genital cancers including ovarian and endometrial cancer. Long term exposure to low concentrations of EDCs may exert potentiation effect with each other and even with endogenous estrogens and could inhibit enzymes responsible for estrogen metabolism. Exposure time to these EDCs is essential as we have seen from Diethylstilbestrol experience. Dose–response curves of EDCs are also unpredictable. Hence mode of action of EDCs are more complex than previously thought. In the light of these controversies lower doses of EDCs in long term exposure is not harmless.

Possibility of this relationship and this hypothesis merit further investigation especially through in vivo studies that could better show the realistic environmental exposure. With the confirmation of our hypothesis, possible EDCs could be identified and eliminated from general use as a public health measure.

1. Introduction

Estrogens and other steroid hormones are responsible in different stages of embryological development of female reproductive system. Even after the developmental process is completed, estrogens still have critical role on reproductive system and nonreproductive physiological functions as well [1]. Effect of the natural and synthetic estrogens have been studied for a long time but the data regarding estrogen related chemicals and their effects on reproductive system are scarce. Potential role of estrogen related chemicals, namely endocrine disrupting chemicals (EDCs), on reproductive disease has gained attention in medical literature in recent years. In the recently published second scientific statement of the Endocrine Society's regarding EDCs, increase in hormone dependent cancers in recent years was linked to EDCs in the environment [2]. EDCs are hormone like agents that are readily present in the environment, which may alter the endocrine system of humans and animals. Approximately 800 chemicals are known or suspected to have the potential to function as EDC [3]. Endocrine disruption could be caused by xenoestrogens, antiestrogens, antiandrogens, thyroid function disrupters, corticoid function disrupters, heavy metals (cadmium, lead) and others. Particularly xenoestrogens were accused to cause estrogenic end point effects by mimicking 17B estradiol [2,3]. Most commonly encountered xenoestrogens are phytoestrogens, isoflavonoids, parabens, phythalates, Bisphenol A, polychlorinated Biphenyls (PCBs), organochlorine insecticides (DDT) and others.

2. Hypothesis

EDCs are readily available in the environment and long term exposure is inevitable. Exposure to low doses in a chronic manner could cause hormone dependent genital cancers including ovarian and endometrial cancer.

3. What are the consequences of exposure to xenoestrogens?

Detrimental effects of xenoestrogens came to attention after world war 2 only when widespread use of pesticides had been realized to be associated with a declining number of some species and also unusual sexual behavior in some species [4]. With these

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findings, USA banned the use of DDT (dichlorodiphenyltrichloroe thane) and PCBs at 1970s. After Darbre et al. extracted intact paraben molecules from breast tissue in early 2000s [5,6] many of the studies have focused on the topic of association between xenoestrogens (particularly parabens in under arm cosmetics) and breast carcinoma. Today in many European countries and in USA there is a limitation of paraben content in cosmetic products (maximum concentration of each molecule is 0.4% and maximum total concentration is 0.8% of total content, EU Cosmetics Directive 76/768/EEC). Increasing epidemiological data also show that there is an association between xenoestrogenic molecules and benign gynecologic disorders including decreased fertility, endometriosis [7], precocious puberty [8], uterine leiomyomata [9]. Delayed pubertal breast tissue development also has been observed with early life exposure to dioxins [10].

Several pathophysiological mechanisms have been argued on emerging reproductive diseases. It is thought that prolonged exposure to low potency estrogenic chemicals may potentially suppresses hypothalamo–hypophyseal ovulation axis with negative feedback effect and may lead to increased risk of hormone dependent carcinomas (remember the effect of oligo/anovulation on estrogenic state in Polycystic ovarian syndrome) [4]. One example is the prolongation of follicular phase and suppression of midcycle surge of hypophyseal hormones with the ingestion of 45 mg isoflavons from soy proteins [11]. If this stimulation sustains long enough, then hypogonadal state could develop. Steroidogenic enzymes such as 3-Beta Hydroxysteroid Dehydrogenase, 17-Beta Hydroxysteroid Dehydrogenase, aromatases, sulphatases, sulphotranspherases, are the other targets of xenoestrogens and mostly are inhibited by xenoestrogens [12]. While inhibition of sulphotransferases leads to accumulation of free estrogen [13], inhibition of aromateses lead to opposite effect. One of the best known inhibitors of aromatase enzyme are Phytoestrogens. These chemicals may exert dual estrogenic/antiestrogenic effects as well [14]. Apart from central or indirect effects of xenoestrogens increasing estrogenic mileu, xenoestrogens have also direct estrogenic and tumorogenic effects on uterus or other hormone sensitive reproductive tissues and the mechanisms were discussed below.

4. How Xenoestrogens cause hormone dependent cancers?

Estrogens normally activates nuclear Estrogen alpha and beta receptors and regulates the gene expression with binding promoter region via estrogen responsive elements (EREs). Nuclear receptor based response is relatively slow and uses genomic activation of transcription and protein synthesis [12]. As distinct from nuclear response, estrogens can also induce a rapid nongenomic plasma membrane receptor based response through mER alpha, mER beta, GPER (formerly known as GPR30 receptors). These receptors rapidly initiate cascades of chemical signals (specific ions, lipids, cyclic nucleotides, etc.), activate kinases and phosphatases to exert their downstream effects including enzyme and hormone secretion, Ca++ efflux [15,16]. Orphan receptors (without a certain ligand) and estrogen receptor related receptors also mediate the action of estrogens that are not related to rapid response and nongenomic signaling [17].

One of the best known hormone dependent carcinoma is endometrial carcinoma and most of the risk factors associated with its development are related to long term and unopposed estrogen exposure (nulliparity, early onset of menarche, late menopause, anovulation etc.). Estrogens were accused to be potent mitogens because they increase cell proliferation through promoting cell cycle progression from G1 to S phase meanwhile they cause DNA instability and decrease apoptosis as well [18,19]. In physiological process, cyclic secretion of progesterone opposes such estrogenic effects on these cells through ER alpha down regulation [20]. One of the potential unopposed excess estrogen source is xenoestrogens. The estrogenic potency of xenoestrogens is 10^4 times less potent than the ER alpha binding capacity of 17 beta estradiol (E2) [4-Nonylphenol (1.75×10^{-4}), Octylphenol (7×10^{-4}), Bisphenol A (2.3×10^{-4}), Genistein (1×10^{-4})] [21]. Due to this weak estrogenic effect, formerly xenoestrogens were considered to be harmless to human body. After different estrogenic receptor mechanisms were discovered, this issue was reevaluated and it was shown that xenoestrogens might be much more potent via the non-nuclear (nongenomic, membrane initiated) mechanisms [17]. Unfortunately pathways of nongenomic signaling in estrogen physiology have not been completely understood and needs to be further studied. Xenoestrogenic pathways of nongenomic mechanisms are also remained to be elucidated. What we know is that through this nongenomic rapid mechanism, low levels of different xenoestrogenic molecules can cause estrogenic effect equal to endogenous hormones [22]. Moreover there is also evidence that mixtures of several low level estrogenic chemicals exert their effect additively and synergistically with each other and even with endogenous estrogen [23–25]. Due to the common receptor mediated mechanism it is logical to think that these xenoestrogens exert same low dose effect like natural hormones do even though these exogenous hormones use different receptor signaling. This low dose effect is the classical way of hormonal action in human body similar to estrogens. But unlike endogenous estrogens, of which only a small portion is bioavailable, all of the xenoestrogens present in the circulation could be physiologically active [22]. This higher bioavailable component concept also supports the estrogenic effects of aforementioned chemicals, but in our opinion, potentiation effect of endogenous estrogens discussed above is one of the most important way to cause increased estrogenic activity responsible for indirect proliferative/carcinogenic effect of xenoestrogens in tissues.

5. Evidence in favor of the hypothesis

Emerging data regarding xenoestrogen exposure and reproductive tract carcinoma development reveals conflicting results. Bisphenol A could display carcinogenic properties in a similar manner to estrone and estradiol by causing mutations in sensitive regions in DNA [26]. Moreover, in a study evaluating early fetal life exposure to Bisphenol A, over-expression of estrogen receptor-α and progesterone receptor was detected in the endometrial structures of adult mice [27]. It is thought that estrogen receptor over expression may lead to increased sensitivity to endogenous estrogens [28]. Not only Bisphenol A but also another xenoestrogenic chemical Nonylphenol was shown to influence endometrial cancer development through activation of pregnane X receptor, which is highly expressed in human endometrial cancers [29,30]. Conversely in a study from Japan, authors showed that serum Bisphenol A levels were higher in premenopausal women with normal endometrium than women with endometrial hyperplasia or carcinoma [31]. These findings were unexpected and were explained by the authors that lower Bisphenol A levels could be favorable for neoplastic endometrial tissue growth, in other words Bisphenol A may have antiestrogenic properties in some environmental situations. In their previous study they already showed that Bisphenol A acts as an antiestrogen in the presence of certain level of estradiol through Estrogen receptor-alpha [32]. Phytoestrogens also exert estrogenic and antiestrogenic properties. Genistein, one of the natural phytoestrogen, has a proliferative effect on cells at low concentrations (0.1–10 mM) but has an inhibitory effect when the exposure occur at high doses (>10 mM) as well [33]. Unrelated to the dose effect, some phytoestrogen, such as flavones and isofla-