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ESTROGENS AND ORGANOCHLORINE XENOESTROGENS AND BREAST CANCER RISK

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Abstract. Breast cancer is responsible for considerable morbidity and the majority of female deaths in industrialized countries. In the etiology of breast cancer many endogenous and exogenous risk factors have been discussed. It is estimated that about 40% of all cancers in women are hormonally mediated. Both estrogens and androgens play critical roles in the development of breast cancer, which has been confirmed by numerous epidemiologic data on the levels of serum and urine hormons in populations at low and high risk, as well as by case-control and cohort studies.
Estrogen carcinogenesis is attributed to receptor-mediated growth and proliferation of breast epithelial cells and to DNA impairment caused by activated estrogen metabolites, e.g., catechol estrogens and free radicals.
In the last decade, the organochlorine chemicals, which include pesticides, polychlorinated biphenyl congeners and other representatives of the dioxin family, have been regarded as xenoestrogens. These chemicals are capable of modulating hormonally regulated processes and inducing changes in growth factors that may be responsible for carcinogenic effect. Many case-control studies have shown the distinct association between breast adipose tissue concentrations of several organochlorine xenoestrogens and breast cancer risk. Also in some studies, the women with breast cancer had higher organochlorine levels in serum as compared with controls.

Key words:
Risk factors, Breast cancer, Endogenous estrogens, Estrogen metabolism, Xenoestrogens, Organochlorines

INTRODUCTION

Each year breast cancer is diagnosed in 910 000 women worldwide, and 376 000 women die from this disease. Most of the cases are recorded in highly industrialized countries, (220 000 in Europe and 180 000 in North America) [1]. The annual incidence rate of breast cancer per 100 000 women in Poland during 1983–1987 was the lowest amongst European countries [2]. In 1986–1990 the annual mean number of deaths and standarized mortality rate (SMR) from breast cancer in this country were 4043 and 15.5 per 100 000 women, respectively [3]. In Germany, the mortality rate from breast cancer in 1993 was 44 per 100 000 women [4]. In the United States the overall rate of breast cancer in white post-menopausal women was 4.3 per 1000 person-years [5].

Many endogenous and exogenous factors have been discussed with relevance to breast cancer etiology. Early menarche and late menopause maximize the number of ovulations, hence the cumulative estrogen exposure to the breast epithelium. It is believed that approximately a 20% decrease in breast cancer risk results from each year of delayed menarche. Women who reach natural menopause below 45 years of age are assessed to be at the risk of breast cancer twice as low as that in women who reach menopause at the age above 55 years [6]. This suggests that high serum levels of estradiol, estrone, progesterone,

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or all of them in pre-menopausal women elevates the breast cancer risk in comparison with the much lower levels of these hormones in post-menopausal women.

The primary source of estrogens in post-menopausal women is the conversion of androstenedione to estrone in adipose tissue. Thus, post-menopausal obesity increases the risk of breast cancer through increased production of estrogens. Obesity is also associated with diminished sex hormone-binding globulin (SHBG) production, and elevated proportion of free- and albumin-bound estradiol as the biologically active estrogen [7].

The protective effect of early age at birth of the first child is complex. During the first trimester of pregnacy, the level of free estradiol increases rapidly. However, in the next trimestrs of pregnancy, both prolactin and free estradiol levels are diminished, while SHBG concentration is increased, giving overall benefit with respect to reduced breast cancer risk [7]. Prolonged lactation and physical activity can reduce the number of ovulatory cycles. It was found that the risk of breast cancer among women who exercised at least 4 h per week during their reproductive years was nearly 60% lower than that of inactive women [8]. Also an inverse association between concentration of serum estrone and physical activity was reported [9].

There is a striking variation in breast cancer incidence in different countries. The highest reported rates of breast cancer incidence are for white or Hawaiian women in the United States whereas significantly lower rates are reported for women in Asia and Africa [1]. The second and third generations of female descendants of migrants from low-risk to high-risk regions experience rates of breast cancer incidence almost similar to those of the host country [1], clearly implicating lifestyle factors as the major contributors to the development of the disease. It has also been suggested that dietary and environmental factors may be responsible for up to 50% of breast cancer incidence [10]. A low-fat diet [11], and a vegetarian diet [12] have been shown to reduce levels of sex-steroid hormones. The above mentioned data suggest that reduction of serum hormone concentrations may decrease the breast cancer risk.

ENDOGENOUS ESTROGENS AND THEIR METABOLISM

There is a view that about 40% of all cancers in women are hormone mediated [13]. Both estrogens and androgens play critical roles in the development of breast cancer [14]. Epidemiological evidence of the role of endogenous estrogens in breast cancer etiology have come from numerous studies of serum and urine hormone levels in populations at low and high risk, and from case-control and cohort studies. Higher levels of serum estrone and estradiol in post-menopausal white women in the USA, compared to post-menopausal women living in rural areas in Japan were found [15]. Similar results were obtained in the study of post-menopausal cases of breast cancer compared to controls in Los Angeles [16].

In a population-based case-control study which included 122 pairs of post-menopausal women, a positive association with serum estrone (odds ratio (OR) = 1.20, 95% confidence interval (CI): 0.93–1.55), androstenedione (OR = 1.32, 95% CI: 1.05–1.65), and inverse association with SHBG (OR = 0.71, 95% CI: 0.48–1.04) after adjustment for hormonal variables and body mass index (BMI) were observed [17].

In another study, free estradiol, albumin-bound estradiol and estrone were all associated with the increased risk of breast cancer after adjusting for BMI among 130 cases and 251 controls in a prospective examination [18]. After comparing the highest quartile to the lowest quartile, the adjusted OR for free estradiol was 2.9 (95% CI: 1.3–6.6), for albumin-bound estradiol – 3.3 (95% CI: 1.4–7.4), for estrone – 2.5 (95% CI: 0.8–7.8), and comparing the third to the first quartile for estrone was 3.7 (95% CI: 1.4–10.2).

There is evidence that post-menopausal women who develop breast cancer also show relatively high serum concentrations of other sex hormones, especially testosterone, dehydroepiandrosterone sulfate (DHEAS) and androstenedione. These hormones are precursors of estrogens. Among 24 post-menopausal breast cancer patients and 88 matched control subjects, the serum levels of total estradiol, DHEAS, total testosterone and free tes-

tosterone were higher, and the levels of SHBG were lower in patients than in controls [19]. The age-adjusted relative risk (RR) of breast cancer was 5.5 (95% CI: 1.5–22.2) for total estradiol, 7.0 (95% CI: 1.4–36.4) for total testosterone, 5.7 (95% CI: 1.5–22.2) for free testosterone, 2.6 (95% CI: 0.6–11.1) for DHEAS and 0.3 (95% CI: 0.1–1.3) for SHBG.

In a case-control study which included 97 white women with confirmed incident breast cancer and 244 randomly selected controls, 65 years of age or older, the RR of breast cancer in women with the highest concentration of bioavailable estradiol and free testosterone was 3.6 (95% CI: 1.3–10.0) and 3.3 (95% CI: 1.1–10.3), respectively in comparison with those with the lowest concentrations of both hormons [5].

Relatively few studies have reported on estrogens and breast cancer risk in pre-menopausal women. The two earlier studies noted insignificant differences in estradiol levels between cases and controls [20,21]. More recent studies suggested that mean estradiol concentrations may be higher in cases than in controls, but were found not statistically significant in either of these studies [22,23].

All in all the above mentioned results support the hypothesis that endogenous estrogens play a crucial role in breast carcinogenesis. This is in spite of the well known variations of hormone levels caused by chronobiological phenomena, age, disease status, etc.

Estrogen carcinogenesis can be attributed to: (i) estrogen receptor-mediated growth and proliferation as a result of the hormone ability to stimulate the expression of genes encoding for different growth factors, e.g., 16α-hydroxyestrone [24], and (ii) DNA impairment [25] and formation of adducts derived from activated metabolites, e.g., catechol estrogens and free radicals, e.g., hydroquinones or quinones generated during estrogen metabolism [26,27].

Cytochrome P450 (CYP)-dependent enzymes present in human mammary epithelial cells [28] participate in the oxidative metabolism and activation of endogenous estrogens, i.e., estrone and 17β-estradiol. The expression levels of CYP enzymes are up to 500 times lower in the breast tissue than in the liver [29]. CYP1A1 catalyzes the hydroxylation of estrogen at the C-2 position [30]. CYP1B1 hydroxylates 17β-estradiol at the C-4 position to 4-hydroxyestradiol [31], which is further activated to reactive semiquinone/quinone intermediates and their free radicals (Figs. 1 and 2).

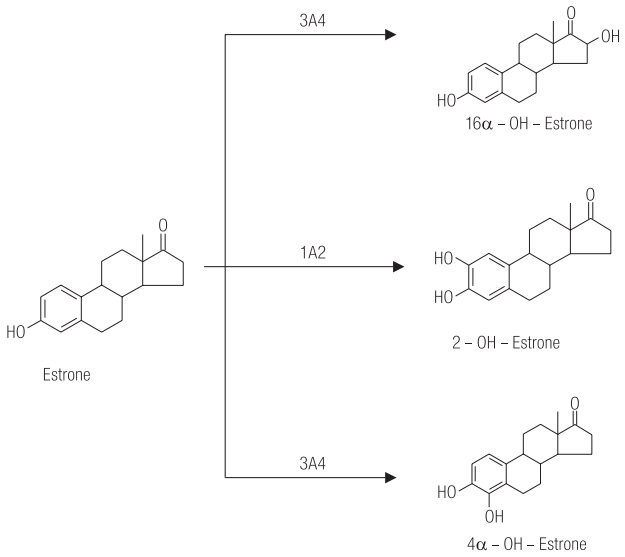

Fig. 1. The metabolic activation of estrone [32].

There is evidence of the existence of polymorphism in the genes encoding CYP1A1, CYP1A2, CYP3A4, and CYP1B1. For example, at least six different variants of CYP1B1 gene were described. Some products of this gene exhibit altered kinetics with distinctly lower or higher K_m values for both 2- and 4-hydroxylation of 17β-estradiol [33,34]. For example, CYP1B1*2 gene product does not appear to differ significantly from the wild-type in terms of 17β-estradiol hydroxylation, but in the case of the CYP1B1*3 product, a lower K_m value for both 2- and 4-hydroxylation has been observed [34]. So, CYP1B1*3 gene product with a lower K_m value for hydroxylation of this hormone at both mentioned positions is particularly interesting. The normal plasma levels of 17β-estradiol are approximately two-fold lower than CYP1B1 K_m values, and it is likely that they are functionally relevant to higher levels of potentially carcinogenic catechol estrogens. In a study of 84 cases and 103 controls, the carriers of the CYP1B1*3 allele were more frequent among breast cancer women with OR = 2.32 (95% CI: 1.26-4.25) adjusted for age, age at menarche, age at first full-term pregnancy, BMI, and smoking status, than those in controls [35].

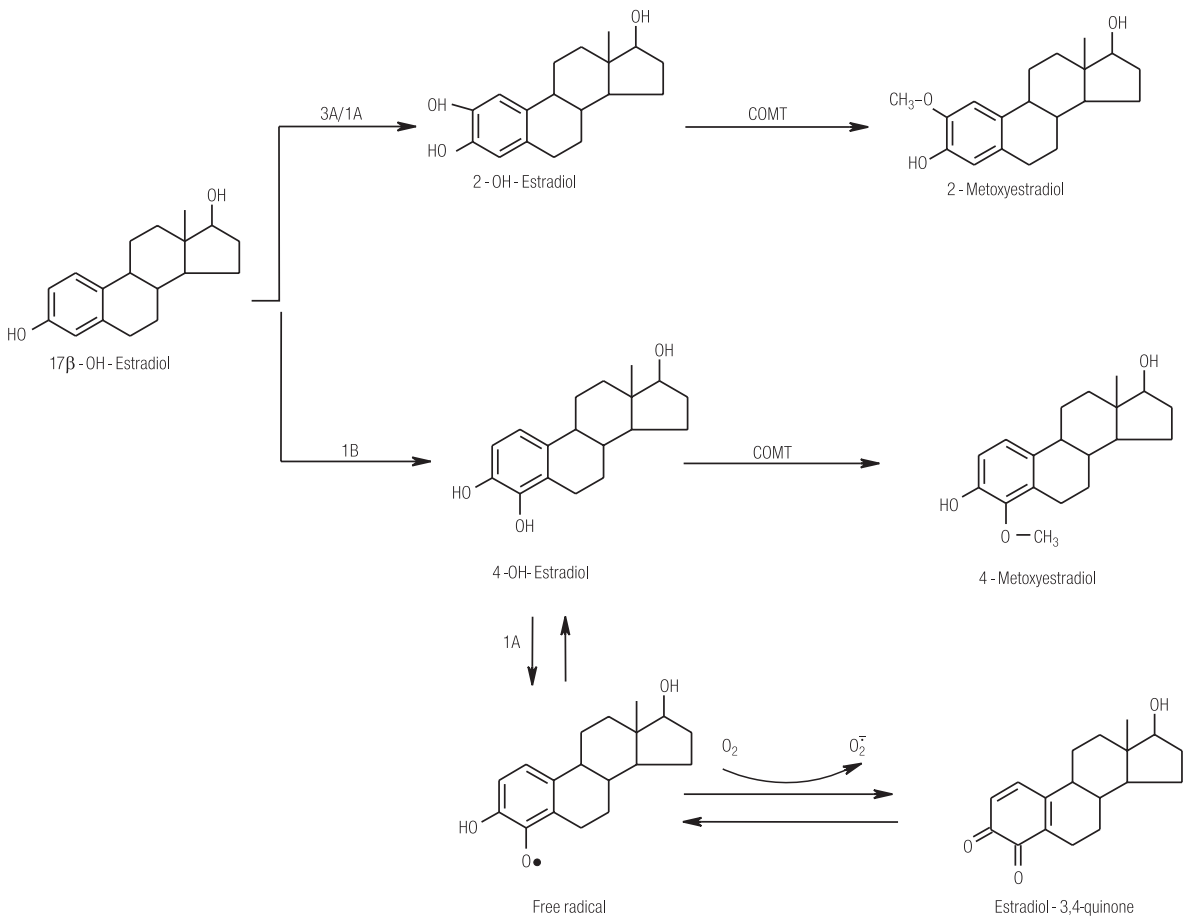

Fig. 2. The metabolic activation and detoxification of 17ß/estadiol [36].

Thus, the CYP1B1*3 variant was positively related to the susceptibility to breast cancer and was specific to women with higher BMI values.

Also human CYP2C enzymes have been shown to catalyze the hydroxylation of estradiol to form catechol estrogenes [37]. The available data indicate that 2- and 4-catechol estrogens may regulate hormonal action in the hypothalamus, pituitary, and uterus [38], and may play a significant role in the breast carcinogenesis after their metabolic activation to semiquinone, quinone, and free radicals.

Hepatic CYP2E1 involved in small molecule metabolism [39] is induced by ethanol, but the regulation of mammary expression of this enzyme has not been investigated. Moderate ethanol consumption is associated with slightly elevated breast cancer risk in women [40]. It is uncler whether this effect results in increased endogenous estrogen levels or in their metabolic activation.

Enzymes from the CYP3A family are most important in hepatic drug metabolism because of their wide substrate specificity. CYP3A catalyzes the hydroxylation of estrone to 16α-hydroxyderivative, a metabolite involved in breast cancer induction [25]. CYP3A4 and CYP3A5 mRNAs have been detected in mammary tissues [41].

CYP 19, so called a steroid aromatase, mediates the rate-limiting step in the metabolism of C19 androgen steroids to estrogens. This CYP and its mRNA have been found in the epithelial cells of the terminal ductal lobular units and surrounding stromal cells of the normal human breast [42]. The high activity of this enzyme may increase breast cancer risk [43], probably by providing more estrogen for activation to genotoxic metabolites and by stimulating breast epithelal cell mitosis.

Other oxidative enzymes may also participate in metabolic activation of estrogens. Lactoperoxidase and myeloperoxidase have been involved in mutagenic and carcinogenic

activation of estrogens in the human breast tissue [44]. Lactoperoxidase mRNA was identified in mammalian tissue [45]. It was found that bovine lactoperoxidase activates 17β-estradiol [46], 4-hydroxycatechol estrogens [47], and causes free radical-induced DNA damage during oxidation of polychlorinated biphenyls (PCBs) [48]. Myeloperoxidase present in breast milk is responsible for the epoxidation of cholesterol into mutagenic, and probably carcinogenic intermediates in breast tissue [49].

Although cyclooxygenase (COX) and lipoxygenase can cooxidize the polycyclic aromatic hydrocarbon benzo[a]pyrene into reactive intermediates [50,51], it is yet unclear whether these activation pathways are significant in estrogen metabolism in human mammary gland.

Several conjugated enzymes are involved in estrogen metabolism. Catechol O-methyltransferase (COMT) rapidly methylates catechol estrogens at the 2-, 3-, or 4-hydroxy position [52] (Fig. 2). COMT is expressed in the liver, kidney, breast, erythrocytes, and endometrium [53]. With increased catechol biosynthesis or decreased COMT activity, these catechols are easily oxidized to reactive semiquinones and quinones, which exert genotoxic and cancerogenic effects.

A genetic polymorphism (guanine → adenine), creating a valine (Val) → methionine (Met) [COMT(Val) → COMT (Met)] substitution at codon 158, is associated with low enzyme activity. It was suggested that its carriers, about 25% of caucasians, may be at increased breast cancer risk. In a study of 281 cases and 289 controls, a significantly higher risk for pre-menopausal breast cancer with COMT(Met/Met) genotypes (OR = 2.1; 95% CI: 1.4–4.3), compared with the homozygotes COMT(Val/Val) genotype women, was observed [54]. Women with high BMI and the COMT(Met/Met) genotype were found to be at especially high breast cancer risk (OR=5.7; 95%CI: 1.1–30.1). A study in Taiwanese women (150 cases and 150 controls), focused on estrogen metabolism, found that of the three gens, i.e., CYP 17, CYP1A1, and COMT, low activity of COMT genotype was associated with the highest relative risk of breast cancer (RR = 4.0; 95% CI: 1.12–19.8) [55].

UDP-glucuronyltransferases are involved in estrogens [56] and androgens [57] glucuronidation as a major pathway metabolism of these hormones in the breast. Glucuronidation produces polar conjugates that are readily excreted from organism. Polymorphism resulting in altered glucuronidation activity has been identified [58], but the effect of these polymorphisms on breast cancer risk have not been reported.

Sulfotransferases (SULTs) include estrogen SULT and the hydroxysteroid SULTs, encoded by SULT1 and SULT2 genes, respectively. These enzymes inactivate estrogens, because the introduction of the sulfate group prevents the binding of the steroid to its receptor, and thus reduce its mitogenic effects [44]. Although the chemical consequences of sulfation are well known for estrogen, the consequences of desulfation are not fully defined although may have biological relevance.

Glutathione S-transferases (GSTs) play an important role in detoxication processes as peroxidases and as enzymes responsible for glutathione transfer to hydrophobic electrophils. There are six major gene families (A, M, P, S, T, and Z) encoding six enzyme proteins with overlapping substrate specificities [59]. In human breast tissue, the expression of π, μ, and αGST isoforms has been detected [60]. It was found that of these three isoforms, two enzymes have glutathione peroxidase activity, one selenium-dependent and one selenium-independent. While the selenium-dependent isoform can reduce both hydrogen peroxide and organic hydroperoxides, the selenium-independent isoform can only metabolize organic hydroperoxides.

Polymorphism of many GST genes in some cases results in the absence of the gene in some persons, (e.g., GSTM1 genotype). The results of epidemiological studies on the role of GSTs in breast cancer risk are inconsistent. In a study of 110 cases and 113 controls, an increased breast cancer risk in women with the GSTM1 null genotype (OR = 2.10; 95% CI: 1.22–3.64) was observed [61]. In a French caucasian population study (361 cases and 437 controls) [62], and also in a United States study (740 cases and 810 controls) [63], no associations between the null genotype and breast cancer risk were found.

Other detoxication enzymes, especially epoxide hydrolase and N-acetyltransferases, do not seem to play a significant role in breast cancer risk associated with estrogens.

ORGANOCHLORINES AS XENOESTROGENS

Estrogens are substances which can directly elicit the stimulation of mitotic activity in the tissues of the female genital tract. The induction of mitotic effect by estrogens is considered to be a multistage process that is vulnerable to disruption at many stages. The following five stages of this process are identified: estrogen receptor binding, transcription, macromolecule synthesis, cell proliferation, and clinical consequences. The binding of the estrogens (ligands) to estrogen receptors (ERs) increases the affinity of the ERs to estrogen-specific response elements (EREs) on the DNA of target genes. The complex ligand-ER-ERE and inducible gene determine stable transcription complex, and the initiation of transcription. It is manifested by the synthesis of macromolecules, which include mRNAs, proteins (growth factors, oncoproteins, estrogen, progesterone receptors), and DNA. Cell proliferation takes place as a manifestation of transcription. Finally, clinical consequences may occur, which include tissue enlargement, uterine abnormalities, change in sex ratios, decrease in reproductive cells, disruption of reproductive cycles, and developmental abnormalities [64].

In 1993, the first study on the association between organochlorine levels in human serum and breast cancer risk was reported [65].

Organochlorines, a class of about 15 000 organic compounds, include insecticides e.g., 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT), hexachlorocyclohexane (HCH) isomers, methoxychlor, toxaphene (polychlorinated camphenes), and also polychlorinated biphenyl congeners (PCBs), as well as other representatives of the dioxin family. These compounds were widely used in the past in agriculture and industry. Some of them are resistent to degradation and very lipid soluble, therefore, persist in the environment, biocumulate and biomagnify the food chain to humans. These chemicals are commonly known as so called persistent organic pollutants (POPs).

The general population is exposed to POPs mainly through foods of animal origin and also through water, ambient and indoor air, dust, and soil. As a result, several POPs are detectable in most human sera, adipose tissues, and breast milk [66–68]. Human breast tissue is a site for accumulation and biomagnification of POPs [69–71]. The levels of these chemicals increase as a function of age [71–73].

POPs have the capacity to modulate hormonally regulated processes and induce changes in growth factors that may be responsible for immunotoxic, neurotoxic, teratogenic, and cancerogenic effects. These environmental pollutants act by mimicking or inhibiting endogenous hormones action, modulating the production of endogenous hormones, or altering hormone receptor population [74,75]. Due to the ability of these chemicals to interfere with the endocrine system, they have been labeled as "endocrine disruptors". The major mechanisms of endocrine disruption are binding xenoestrogenes to the estrogen receptor (ER), inhibition or stimulation of hormone metabolism, actions involved in the regulation of various neural centers, or alterations in serum hormone-binding proteins [76,77].

Although organochlorine xenoestrogens are generally less potent than endogenous estrogens when tested in bioassays and expressed by IC_{50} or RBA values (Table 1), they are the subject for concern due to their ubiquity in the environment, their inefficient metabolism and long half-life in the environment and organism as well as their long-term sequestration in adipose tissues. In fact, the levels of organochlorines in fat are about 100–300 times higher than those measured in serum [78]. They are excreted chiefly through lactation [66].

In the studies of the relationship between organochlorine xenoestrogens and breast cancer risk, the measure of these chemicals in breast adipose tissue is recommended for at least two reasons. Firstly, even small samples of adipose tissue contain organochlorine chemicals in the detectable range, and from analytical point of view, are more suitable for specific analyses, especially those of congeners, which are important because individual chemicals have been shown to have different biological activity. Secondly, organochlorines measured in breast adipose tissue provide real dimension of cumulative internal exposure at the target site for breast cancer, independently of the sources and routes of exposure.

Table 1. A 50% inhibition of (^{3}H)17β-estradiol binding (IC_{50}) and relative binding affinities (RBA) for some steroid estrogens and organochlorine xenoestrogenes

Compound	Purity (%)	IC_{50} (Mean ± SEM)	RBA (%)
17β-Estradiol	NA	$8.99 \cdot 10^{-10} \pm 0.27 \cdot 10^{-10}$	100.00
Estriol	99	$9.25 \cdot 10^{-9} \pm 1.75 \cdot 10^{-9}$	9.72
Estrone	99	$1.23 \cdot 10^{-8} \pm 0.32 \cdot 10^{-8}$	7.31
17α-Estradiol	99	$2.93 \cdot 10^{-8} \pm 0.82 \cdot 10^{-8}$	3.07
3-Deoxyestradiol	NA	$1.80 \cdot 10^{-7} \pm 0.20 \cdot 10^{-7}$	0.50
3-Deoxyestrone	NA	$1.43 \cdot 10^{-5} \pm 0.58 \cdot 10^{-5}$	0.006
DDT isomers and metabolites:			
o,p'-DDT	98.5	$6.43 \cdot 10^{-5} \pm 0.89 \cdot 10^{-5}$	0.001
o,o'-DDD	99.2	$>3.00 \cdot 10^{-4}$	–
p,p'-DDD	98.5	$>1.00 \cdot 10^{-4}$	–
o,p'-DDE	99.8	$>5.00 \cdot 10^{-4}$	–
p,p'-DDE	99.4	$>1.00 \cdot 10^{-4}$	–
p,p'-DDT	99.2	$>1.00 \cdot 10^{-3}$	–
Methoxychlor	95.0	$1.44 \cdot 10^{-4} \pm 0.66 \cdot 10^{-4}$	0.001
PCBs:			
2',3',4',5'-Tetrachloro-4-biphenylol	95.0	$3.95 \cdot 10^{-7} \pm 0.15 \cdot 10^{-7}$	0.228
2',5'-Dichloro-4-biphenylol	95.0	$2.50 \cdot 10^{-6} \pm 0.30 \cdot 10^{-6}$	0.036
2, 4'-Dichlorobiphenyl	99.0	$3.65 \cdot 10^{-4} \pm 1.15 \cdot 10^{-4}$	0.0002
2, 2',4, 4'-Tetrachlorobiphenyl	98.4	$> 1.00 \cdot 10^{-4}$	–

SEM – standard error of the mean.
NA – purity not available.
Source: Adapted from [76].

To evaluate the association between breast adipose tissue concentrations of several organochlorine xenoestrogens and breast cancer risk, many case-control studies have been conducted (Table 2). In all epidemiological studies, presented in Table 2, women with breast cancer had higher levels of organochlorine chemicals, including dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), some PCB congeners, and octachlorodibenzo-p-dioxin (OCDD), in comparison with suitable control groups [79]. Also breast cancer risks associated with these chemicals, verified for other breast cancer risk factors, were clearly increased.

A considerable number of epidemiological studies of breast cancer risk in relation to plasma/blood organochlorine xenoestrogen concentrations have been published in recent years. In some of them, women with breast cancer had higher levels of some chlorinated chemicals, including total PCBs, DDE, and dieldrin compared with controls [65,83,84]. The obtained data suggest that exposure to some organochlorines, such as dieldrin with estrogenic properties, may not only increase the risk of breast cancer but also significantly reduce the survival [85]. In other studies, neither the differences in the organochlorine concentrations nor the association between total PCBs, the same PCB congeners, DDT, DDE, β-HCH, and HCB concentrations and breast cancer risk were observed as compared with controls [86–91].

Many potential risk factors of breast cancer, including age, BMI, age at birth of the first child, parity (ever vs never), lactation history, menopausal status and estrogen receptor status, are taken into consideration [84]. The latter is especially important in case of organochlorines possessing estrogenic properties, such as DDT, coplanar PCBs, and HCB. The highest risk in pre- or post-menopausal women

Table 2. Human epidemiologic studies on organochlorine xenoestrogens in adipose breast tissue and breast cancer risk

Total Cases/Controls	Xenoestrogen	Xenoestrogen concentration		OR (95% CI)	References
		Cases	Controls		
20/20	DDE	2200 (1470)[d]	1487 (842)[d]	–	[70]
165/54					[73]
54/20	DDE	1848 (1536)[d]	890 (645)	5.65 (1.74–18.34)	
61/13	HCB	61 (29)[d]	47 (23)[d]	2.3 (1.02–5.15)	
61/12[b]	HCB	69.5 (29.4)[d]	55.3 (28.5)[d]	4.56 (1.15–18.08)	
32/21					[80]
11/6[c]	HCB	87.3 (23–490)[d]	55.9 (17–400)[d]	7.1 (1.1–45)	
8/2[c]	PCB-77	5.1 (1.2–9.8)[e]	2.8 (0.7–5.3)[e]	33 (1.8–588)	
69/65	PCB-28	–	–	9.6 (3.8–24.4)	[81]
217/213					[82]
20/19[a]	PCB-105	> 6.2[d]	≤ 4.1[d]	3.9 (1.7–8.9)	
28/20[a]	PCB-118	> 28[d]	≤ 16[d]	2.85 (1.24–6.52)	
51/27[b]	PCB-170	24-34[d]	≤ 23[d]	3.27 (1.44–7.44)	
46/31[b]	PCB-180	52-71[d]	≤ 51[d]	2.43 (1.09–5.43)	

Xenoestrogen concentrations are expressed as mean ± standard deviation or range values.
a – pre-menopausal women.
b – post-menopausal women.
c – post-menopausal women, ER+.
d – ng/g lipid.
e – pg/g lipid.

with estrogen receptor-positive (ER+) breast cancer was associated with DDE [92] and co-planar PCBs [80] in organism. Also, an endocrine effect has been reported for HCB [93].

How organochlorine xenoestrogens participate in carcinogenesis is not known in detail. Some of them are able to induce CYP enzymes and thereby to disturb the hydroxylation pathway of metabolism of endogenous estrogens [94]. It was found that organochlorine pesticides decreased the amount of 2-hydroxyestrone produced, and markedly increased the amount of 16α-hydroxyestrone formed in MCF-7 cells from ER+ human breast cancer cell cultures. The greatest effects were observed with DDT, o,p-DDE, kepone, and atrazine, which caused significant increase in the ratio of C-16α/C-2 metabolites [95,96]. It is known that 16α-hydroxyestrone, a fully potent estrogen, increases cell proliferation and exerts genotoxic and tumorigenic effects [97]. On the contrary, 2-hydroxyestrone is a weak antiestrogenic and nongenotoxic catechol estrogen [98]. Clinical studies suggest that these alterations may represent an early event in the multistep process of chemical carcinogenesis [99].

Other organochlorines have a steroid-like three-dimensional structure that facilitates estrogen receptor binding. For example, dieldrin has been shown to bind to the estrogen receptor and to stimulate breast cancer cell growth [77]. The additive combined proliferative effect of o,p'-DDT, p,p'-DDE, β-HCH, and p,p'-DDT mixtures in MCF-7 cells was observed [100].

In addition, the inhibition of gap junctional, intercellular communication in normal breast epithelial cells after treatment with organochlorines, supports the hypothesis that these chemicals have a cancer-promoting potential in human breast tissue [101].

Organochlorine compounds, polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) exert antiestrogenic effects both *in vivo* and *in vitro* [102]. These compounds should thus lower the risk for breast cancer. The risk for breast cancer in women occupationally or environmentally exposed to PCDDs and PCDFs has been reported in few papers.

A standard incidence ratio (SIR) of 0.9 was reported among Danish women with occupational exposure to herbicides contaminated by TCDD [103]. No increased risk

was observed for breast cancer in women occupationally exposed to chlorophenoxy herbicides, chlorophenols, and dioxins (SIR, 0.9; CI: 0.4–1.9) [104]. In the Seveso areas, most heavily contaminated by TCDD, diminished incidence of breast cancer was reported (RR=0.5, CI:0.1–3.3; 0.7, CI: 0.4–1.4, and 1.1, CI: 0.9–1,3 in zone A, B, and R, respectively) [105].

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