

*review*

## Environment and breast cancer – the role of xenoestrogens in breast cancer carcinogenesis

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**Background.** The survival rate of breast cancer patients has not changed much in the last few decades in developed countries. In order to improve the efficacy of breast cancer prevention and treatment, the role of xenoestrogens in the mechanisms of its development has been evaluated. These industrial chemicals bear little structural resemblance to each other and bind to the oestrogen receptors of exposed cells and/or trigger oestrogenic responses in laboratory test systems. Exposure to xenoestrogens has been regarded as a risk factor for carcinogenesis and a preventable cause of breast carcinoma. Several epidemiological and experimental studies in *in vivo* and *in vitro* conditions of the influence of xenoestrogens on the occurrence of breast cancer have been conducted in the last decades and have shown ambiguous results.

**Conclusions.** No increase in breast carcinoma incidence could be found in women who were exposed to relatively high concentrations of xenoestrogens for extended periods and small quantities of these compounds that are present in the environment probably cannot act as etiological agents for the occurrence of this disease. A multi step approach is suggested regarding the sequence of studies and measures that should be taken to further assess the importance of xenoestrogens on breast cancer carcinogenesis.

*Key words:* breast cancer; xenoestrogens; carcinogenesis

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### Introduction

The word cancer is used to describe several diseases that are caused by multiple genetic changes in the cells of different tissues. These changes may only manifest themselves after several years, causing the proliferation and immortalisation of affected cells. The clinical consequences of these changes are specific clinical states which lead to the premature death of 25-30% of the population.<sup>1</sup> The improvement of survival in cancer, particularly breast cancer, the survival rate of which

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has not changed significantly in the last few decades in the developed countries, is thus among the declared goals that were set to improve the health of the whole population by the year 2000.<sup>2</sup> The relative five-year survival rate of breast cancer patients in the United States (US) was practically constant at slightly less than 80% for the 1974-1987 period.<sup>1</sup> The relative five-year survival rate for the patients with this disease who were diagnosed in the 1977-1985 period in Southern Australia was 72.8%; however, patients who had breast cancer diagnosed there in the consequent 1986-1994 period had only slightly improved survival rate of 78%.<sup>3</sup> In order to further improve the efficacy of breast cancer prevention and treatment, conditions and mechanisms that lead to its development must be known. An especially critical assessment of the significance of and role played by environmental risk factors is therefore necessary. According to some sources, xenoestrogens, industrial chemicals that bear little structural resemblance to each other and that bind to the oestrogen receptors (ER) of exposed cells and/or trigger oestrogenic responses in laboratory test systems, are among these factors.<sup>4</sup>

### Xenoestrogens and breast cancer

#### *Breast cancer: some characteristics*

By definition, breast cancer is a disease in the course of which malignant proliferation of the epithelial cells in lobules and ducts of the breast tissue takes place.<sup>5</sup> However, this definition could be regarded as too limited since breast cancer is a field researched by experts that are not necessarily specialised in cell and tissue pathology. Breast cancer is the second most frequent form of cancer affecting women, non-melanocytic skin cancer being the most frequent.<sup>6</sup> It is also the most common cause of death for female cancer patients,<sup>7</sup> the incidence of which is up to five times higher in first-world countries than in some less

developed Asian and African countries.<sup>8</sup> Moreover, the incidence of breast cancer in first-world countries still seems to be rising slowly.<sup>1,9</sup>

Histologically, breast cancer is usually a carcinoma that develops in the terminal ductal-lobular units. In most cases, a breast carcinoma develops from ductal cells and less frequently from lobular cells, whereas tumour formations that can be histologically classified as primary sarcoma, lymphoma or unclassified tumours are relatively rare, as are metastatic breast tumours that originate from other organs.<sup>5,10-12</sup> The occurrence and rapid development of breast carcinoma and the associated incidence of this disease in women is connected to the presence of certain risk factors. They include a relatively low age at first menstruation and a relatively high age at menopause, a high age at first birth, obesity and a fat-rich diet, excessive alcohol consumption, and benign breast disease and breast carcinoma in the family's medical history. The importance of oral contraception and postmenopausal hormone therapy for the occurrence and development of this disease is not yet completely clear.<sup>1,5,11</sup> Unfortunately, al-

**Table 1.** Characteristics of patients with symptomatic breast carcinoma at the time of diagnosis

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1. The most common symptom among diagnosed breast carcinoma patients is a lump (present in 90% of cases that exhibit symptoms at time of diagnosis), discovered by the patient during self examination, showering or bathing.
  2. Pain is present in 10% of breast carcinoma patients.
  3. Skin-colour change on the skin of the affected breast, nodules or oedema (peau d'orange) are present in 5-10% of breast carcinoma patients.
  4. Changes on nipples are apparent in 5% of patients, half of which have also exhibited discharge from the breast; with the other half, retraction or eczematoid changes can be observed.
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most 80% of breast carcinoma patients only visit a doctor for the necessary diagnostic procedures after the symptoms and signs of the disease become apparent (Table 1).<sup>5,9,11</sup>

#### *Xenoestrogens and breast carcinoma carcinogenesis*

According to several experts in this field, the increase in breast cancer incidence in recent decades appears to be caused by prolonged exposure to oestrogens. It is a well-known fact that the incidence of breast carcinoma in developed countries has risen the most in the population of post-menopausal women.<sup>4,13,14</sup> Moreover, prolonged exposure to environmental oestrogens is probably a significant risk factor that contributes to the higher incidence of breast cancer in the US compared with the countries of East Asia. The importance of prolonged exposure to oestrogens in connection with cancer can be shown by the fact that, in the US, first menstruation occurs at the average age of 12.8 years whereas in China it occurs at the average age of 17 years.<sup>4</sup> Also noteworthy is the fact that the incidence of breast cancer in immigrants from East Asia and their descendants is practically the same as with women who were born in the US along with several generations of their ancestors.<sup>15,16</sup> Davis et al. set up a hypothesis in 1993 according to which xenoestrogens could be a risk factor for the carcinogenesis of breast carcinoma in women and that prolonged exposure to these compounds could be considered one of the preventable causes of this disease.<sup>4,17</sup> In the last few years, several structurally different xenoestrogens have been discovered which can, due to their tertiary structure and conformation, bind to oestrogenic receptors (ER) or induce oestrogenic responses in laboratory test systems, or can function using both mechanisms at the same time.<sup>18-20</sup> Among xenoestrogens are the halogenated organic compounds that were used until recently as

pesticides. Some better known examples are kepone, toxaphene, endosulfan, dieldrin, *o,p'*-DDT, *p,p'*-DDE, some polychlorinated biphenyl (PCB) mixtures, hydroxy-PCB, nonylphenol and some phthalates.<sup>4</sup>

#### *Epidemiological studies of importance of xenoestrogens for breast cancer carcinogenesis*

Epidemiological research into the importance of xenoestrogens for breast cancer carcinogenesis represents only a part of research on the environmental risk factors that may influence the occurrence and development of this disease, and this is despite a rising awareness of their importance.<sup>21</sup> The studies conducted have mostly been case-control studies and investigated the presence of organic halogenides, i.e. xenoestrogens in breast carcinoma patients compared to healthy control subjects.

The hypothesis that claims xenoestrogens are a risk factor for breast cancer formation and development has been confirmed by some studies but disproved by others.<sup>22-28</sup> According to some earlier studies, no difference was observed in PCB and DDE concentrations in the breast tissues of patients and control subjects. However, PCB concentrations in necropsy samples of breast carcinoma patients were higher than in the necropsy samples of control subjects.<sup>22,23</sup> A study published in 1992 by Falck et al. showed that PCB and DDE concentrations in breast carcinoma patients' breast tissue were higher than concentrations in healthy control subjects.<sup>24</sup> A similar study published later by Dewailly et al. only found higher DDE concentrations in breast tissue. Some groups of breast carcinoma patients had increased serum concentrations of DDE and PCB compared to healthy control subjects,<sup>25</sup> whereas an extensive study published in 1994 by Krieger et al. failed to confirm these differences.<sup>27</sup> In one of the extensive studies that followed, Henderson et al. found a large increase in the serum concentrations of polybrominated biphenyls (PBB)

in breast carcinoma patients compared to the control subjects.<sup>28</sup>

These epidemiological studies were unable to define the importance of xenoestrogens for the carcinogenesis of breast carcinoma, as higher serum concentrations of chlorinated organic compounds may have been, in some studies, caused by specific eating habits, since increased concentrations of these compounds were found in high-fat food as well as fish.<sup>4</sup> It should be noted, however, that the results of these and similar studies have in many cases led the laboratory scientists to seek to elucidate the role of xenoestrogens in the mechanisms of the breast cancer carcinogenesis.

*Studying the importance of xenoestrogens for breast cancer carcinogenesis in experimental in vitro conditions*

Several xenoestrogens that are able to bind to ER (Table 2) have been identified in the last few years using cell cultures in experimental *in vitro* conditions.<sup>4,18-20</sup> By binding to ER, the xenoestrogens could act as sex hormones and accelerate breast carcinoma cell proliferation. In this mitogenic effect, ER play the role of genetic transcription factors that release the block in the G1 phase of the cell cycle.<sup>1</sup>

Other mechanisms of the effects xenoestrogens have on breast carcinoma cells have

also been researched with the help of *in vitro* conditions. The results of some studies indicate that the xenoestrogens reduce the enzymatic activity of 17 $\beta$ -estradiol 2-hydroxylase, and increase the enzymatic activity of E<sub>2</sub> 16 $\alpha$ -hydroxylase, which leads to a change in the ratio of the two respective metabolites in the cell. After exposure to oestrogens, the concentration of 16 $\alpha$ -hydroxyoestrone in the cells is increased and is higher than the concentration of 2-hydroxyestrone, which is why the ratio of their concentrations is increased.<sup>17,29</sup> Previous studies also indicate the importance of the change of the ratio which showed that E<sub>2</sub> 16 $\alpha$ -hydroxylase acts as a strong oestrogen whereas 17 $\beta$ -estradiol 2-hydroxylase is a partial antagonist of the ER receptors.<sup>30,31</sup> In the MCF-7 breast carcinoma cell line, many xenoestrogens (Table 3) have the aforementioned effect on the two hydroxylases,<sup>32</sup> whereas the indole-3-carbinole (I3C), an ingredient of several vegetables, inhibits the development and growth of breast carcinoma in *in vitro* as well as *in vivo* models.<sup>33,34</sup> However, later studies have shown that a change in activity of E<sub>2</sub> 2-hydroxylase in MCF-7 cells is not caused by inducing the P 450 system but is instead a result of this system's direct interactions with various chemical substrates. Moreover, E<sub>2</sub> 2-hydroxylase activity was reduced after adding pure anti-oestrogen ICI 164,384. These results show that

**Table 2.** Xenoestrogens that bind to oestrogenic receptors (ER) (*in vitro* cell cultures)

Toxaphene
Endosulphan
Dieldrin
<i>o,p'</i> -DDT
<i>p,p'</i> -DDE
PCB (mixtures and PCB-like compounds)
Hydroxy-PCB
Bisphenol-A
Nonylphenol
Phthalates

**Table 3.** Xenoestrogens that reduce the enzymatic activity of 17-estradiol 2-hydroxylase and increase the enzymatic activity of 16-hydroxylase (*in vitro* cell cultures: MCF-7 cells)

Endosulphan
Kepone
<i>p,p'</i> -DDE
<i>o,p'</i> -DDE
<i>o,p'</i> -DDT
Atrazine
2,2',4,4',5 pentachlorobiphenyl
7,12-DMBA

modulation of E<sub>2</sub> 2-hydroxylase activity in MCF-7 cells cannot serve as a reliable test for carcinogenic effects of oestrogenic pesticides and other compounds that are thought to promote the occurrence and development of breast carcinoma.<sup>4</sup>

*Studying the importance of halogenated organic compounds in the development of breast carcinoma in experimental in vivo conditions*

Some studies of the importance of halogenated organic compounds and related xenoestrogens in the occurrence and development of breast carcinoma were conducted using *in vivo* experimental models with animals (Table 4). Adding atrazine to Sprague-Dawley laboratory rats decreased the latent period of breast cancer development;<sup>29</sup> a similar study with Fisher laboratory rats showed no changes.<sup>35</sup> The results of the study on the Fisher laboratory rats also indicated that atrazine and related compounds influence the oestrus and regulation of synthesis of the luteinising hormone via non-oestrogenic pathways.<sup>35</sup> Additional studies showed that atrazine and simazine have no oestrogenic effect,<sup>36</sup> while a study done previously found that DDT caused an increase in breast cancer incidence in male Sprague-Dawley rats that were given acetamidophenanthrene at the same time.<sup>37</sup> However, a much earlier study showed that

DDT reduces the incidence of breast tumours induced by dimethylbenzanthracene (DMBA).<sup>38</sup> A review of these studies and examinations cannot prove the validity of the hypothesis of the important role of xenoestrogens in breast carcinoma carcinogenesis, as some halogenated organic compounds and xenoestrogens can both inhibit and accelerate it in *in vivo* conditions.

*Halogenated organic compounds with antioestrogenic activity*

Several of the numerous studies on the importance of xenoestrogens for carcinogenesis and the development of breast carcinoma found that there were some halogenated organic pollutants whose effects were directly opposite to those of oestrogens. One such antioestrogenic compound is 2,3,7,8-tetrachlorodibenzo-p-dioxine (TCDD), which according to some studies slows the occurrence of spontaneous breast and uterus tumours in female Sprague-Dawley rats and the occurrence of breast tumours in immunosuppressed B6D2F1 mice with xenografts of the MCF-7 cells.<sup>39-41</sup> Additional studies confirmed the antioestrogen and antitumor effect of TCDD and some halogenated aromatic hydrocarbons (HAH) in human breast carcinoma cell lines in *in vivo* as well as *in vitro* conditions (Table 5).<sup>42</sup>

**Table 4.** Halogenated organic compounds that play a role in breast cancer development (animal experimental models – *in vivo*)

Compound	Animal model	Result	Reference
Atrazine	Rats (female) (Sprague-Dawley)	A decrease in the latent period of breast cancer development	29
Atrazine	Rats (female) (Fischer)	No change in the latent period of breast cancer development	35
ACTDP and DDT	Rats (male) (Sprague-Dawley)	Increased breast tumour incidence	37
DDT	Rats (female) (Fisher)	A decrease in DMBA-induced breast tumour incidence	28

ACTDP = acetamidophenanthrene; DMBA = dimethylbenzanthracene

**Table 5.** Halogenated organic compounds that act as antioestrogens (in vitro cell cultures and in vivo animal experimental models)

Compound	Animal model	Result	Reference
TCDD	Rats (female) (Sprague-Dawley)	A decrease in the occurrence of spontaneous breast and uterine tumours	39
TCDD	Rats (female) (Sprague-Dawley)	Inhibition of breast tumour carcinogenesis	40
TCDD	Mice (immunosuppressed with MCF-7 xenografts)	A decrease in the occurrence of spontaneous tumours	41
TCDD and HAH	Human breast cancer cell lines	Lower activity of peroxydases and binding of EGRF receptors, smaller amounts of m-RNA	42

TCDD = 2,3,7,8-tetrachlorodibenzo-p-dioxine; HAH = halogenated aromatic hydrocarbons

TCDD acts similarly to the "pure" antioestrogen ICI 164,384, which binds competitively to ER and is an ER antagonist.<sup>43</sup> Both compounds inhibit some of the oestrogenic responses and reduce concentrations of oestrogen-associated proteins in MCF-7 cells. However, TCDD does not bind to ER or receptors for other steroid hormones. Like the various classes of HAH and polychlorinated aromatic hydrocarbons (PAH), it binds to the aryl-carbohydrate receptors that trigger signal pathways similar to those triggered by the other ligand-induced transcription factors.<sup>4, 42</sup> Aryl-carbohydrate receptor agonists, which in addition to TCDD and similar pollutants from the class of halogenated hydrocarbons also include I3C and related hetero-PAH found in vegetables and PAH released with the cooking of fish and meat,<sup>4</sup> inhibit the growth-factor-induced growth of human breast carcinoma cells.<sup>44-45</sup>

#### *Various oestrogenic and antioestrogenic compounds in the diet*

An assessment of the influence of the dietary intake of xenooestrogens on breast carcinoma incidence should also include other compounds with oestrogenic and antioestrogenic effects that may be present in the diet. The characteristics of exposure to halogenated orga-

nic compounds with a weak oestrogenic effect are not known. However, there are estimates for average daily exposure to oestrogenic compounds in the diet according to regular measurements of their concentrations in various kinds of food. As reported by Safe and McDougal, the average daily intake of DDT, DDE, toxaphene and dieldrin is about 2.5 micrograms per day;<sup>4</sup> the average daily intake for other xenooestrogens is not known.<sup>46</sup> Bioflavonoids are an important dietary source of compounds with oestrogenic activity and can be found in most fruits, vegetables, walnuts and hazelnuts. The estimated dietary intake of oestrogenic bioflavonoids may reach up to 1000 milligrams per day. However, the concentrations of oestrogenic lignans in various kinds of foods, which have been found in human serum, are as yet unknown.<sup>46-48</sup> Besides these xenooestrogens, the usual diet contains compounds with antioestrogenic effects, as well as compounds that reduce the probability of breast carcinoma occurrence with other mechanisms. Some of them include various cell antioxidants and terpenoids.<sup>4, 46</sup> Estimates have been made of the dietary concentrations of other halogenated organic compounds with antioestrogenic effects and other compounds that act as aryl-carbohydrate receptor antagonists, such as TCDD, HAH, PAH, and I3C.<sup>49-51</sup>

### **An assessment of the importance of xenoestrogens for breast carcinoma carcinogenesis**

Studies of the occurrence and development of breast carcinoma in the last three decades have implicated exposure to natural or synthetic oestrogens as a risk factor for the occurrence of breast carcinoma in women.<sup>1,4</sup> Since 1993, when Davis et al. set up a detailed hypothesis according to which prolonged exposure to xenoestrogens could be considered a preventable cause for the occurrence of this disease in women, several epidemiological and experimental studies in *in vivo* as well as *in vitro* conditions have been conducted to ascertain the validity of this hypothesis.<sup>17</sup> It is impossible to either prove or deny it even with the collected results of a large number of studies.<sup>4,17</sup>

No increase in breast carcinoma incidence could be found in women who were exposed to relatively high concentrations of PCB and DDT for extended periods.<sup>52</sup> The small quantities of these compounds that are present in the environment probably cannot act as etiological agents for the occurrence of this disease. It should also be noted when studying the prolonged exposure of women to xenoestrogens that an ordinary diet contains several compounds that have been shown to prevent the occurrence and development of breast carcinoma in *in vivo* and *in vitro* conditions. Other xenoestrogen-like pollutants, in addition to various cell antioxidants and terpenoids, have been discovered in the diet, such as TCDD and HAH; these have been shown to act as antioestrogens, unlike other pesticides from the class of halogenated hydrocarbons.<sup>4,49,53</sup>

Also noteworthy is the fact that the intake of weakly oestrogenic pesticides from the class of halogenated hydrocarbons, whether in the diet or in some other way, represents only a minor part of daily exposure to oestrogens. Several women receive relatively high

quantities of potent oestrogenic drugs either through hormone contraception or hormone replacement therapy, yet their risk of breast carcinoma is minimal.<sup>16</sup>

### **Xenoestrogens and breast carcinoma – a public health perspective**

The environment we live in and depend on can influence our health for better or worse.<sup>21</sup> An increasing incidence of breast carcinoma has been observed in most industrially and agriculturally developed countries in the last three decades,<sup>2,5-9</sup> the causes of which are subject to a large number of epidemiological and clinical studies, as well as studies in experimental *in vivo* and *in vitro* conditions. Since pesticides have achieved widespread use in this period due to intensive agricultural production, a study of these industrially made compounds as risk factors is part of these ongoing research projects. Some of these compounds are called xenoestrogens due to the fact that they are a part of the environment and because of their weakly oestrogenic effects.<sup>4,5,17,52-54</sup>

The number of breast carcinoma casualties and their relative five-year survival rate after the diagnosis of the disease have not changed much despite advances in treating the symptomatic disease.<sup>1-3</sup> Although screening programmes using mammography are relatively expensive, several randomised studies have shown that a well-considered application of these programmes reduces the mortality rate of breast carcinoma patients.<sup>1, 2, 10, 11</sup> However, since these programmes cannot lead to an immediate reduction in the mortality rate,<sup>55</sup> it is important that the possibilities of improving the overall situation by applying primary prevention methods are taken into consideration. The fact that several cancer research and treatment institutions are conducting a number of studies on the efficacy of various pharmacological approaches to breast

carcinoma prevention is also important. The publication of results of studies on the chemoprevention of this carcinoma with Tamoxifen has aroused considerable professional and public interest.<sup>56</sup>

A large part of the well-informed public shows concern about the possible influence environmental risk factors may have on the occurrence of various diseases. Part of this public is particularly concerned about problems relating to the occurrence of breast carcinoma and other cancerous diseases in relation to xenoestrogens.<sup>4</sup> Unfortunately, the results of studies of the influence of xenoestrogens on breast cancer occurrence are ambiguous, which makes educating the general public through clear and simple data rather complicated. In spite of this, doctors and other medical professionals in the primary health network should help breast carcinoma patients and everyone else to interpret the danger posed by the presence of xenoestrogens in their environment. They should also consider the possibility, when conducting clinical examinations and examining a medical history, that this disease forms due to a possible prolonged exposure to these chemicals.<sup>1, 2</sup>

Suggestions have been made regarding the sequence of studies and measures that should be taken to assess the importance of environmental risk factors. It is necessary to identify the compound – in this case, one or more xenoestrogens which, due to their presence in the environment, may represent a risk factor. Next, the time of exposure to one or more xenoestrogens, the number of such episodes, and their duration and intensity must be determined. The third step towards such an estimate is to identify the characteristics of acute or chronic exposure to xenoestrogens with regard to breast carcinoma carcinogenesis. Especially important is experimental work in laboratories. The characteristics and importance of the link between exposure to xenoestrogens and the predicted results of exposure must be determined. Finally, the

risk of breast carcinoma carcinogenesis in every woman that has been exposed to environmental xenoestrogens must be defined, as must be the probable consequences of such exposure for a larger population over a longer time period and a calculation of population attributive risk, population attributive risk in percentages and odds ratios. By studying xenoestrogens' role in breast carcinoma carcinogenesis, such an estimate would be difficult to make, since the possible effects of exposure to relatively small concentrations of these compounds in the environment and in the routes of entry should be taken into account. Despite these potential problems, it is necessary to obtain such estimates so they can be used when promoting healthy lifestyles and also in order to introduce and justify all public and individual measures that must be taken to remove or at least reduce the presence of xenoestrogens in the environment. A further reduction in breast carcinoma incidence, and consequentially mortality due to breast carcinoma, could thus potentially be achieved.<sup>1-5,11,46-50,52-54,57</sup>

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