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The impact of xenoestrogens on effectiveness of treatment for hormone-dependent breast cancer – current state of knowledge and perspectives for research

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Abstract

Introduction. Breast cancer is the most common cancer occurring in women and causing the highest number of deaths among them. The role of xenoestrogens has been the subject of many studies in the pathogenesis of breast cancer. Less is known about the impact of xenoestrogens on the effectiveness of hormone therapy used to treat breast cancer, and thus possible drug-xenostrogen interactions.

Objective. The aim of this review is to summarize the current state of knowledge and present perspectives for further research on the impact of xenoestrogens on the effectiveness of drugs used in the treatment of hormone-dependent breast cancer.

Current state of knowledge. Phytoestrogens, in particular flavonoid genistein, are the best studied group of xenoestrogens in terms of interaction with drugs used in the treatment of breast cancer, due to their frequent use, including their use in alleviating the adverse effects of hormone therapy. Analyzing the current state of knowledge, it seems that phytoestrogens intake should be avoided during conventional anti-cancer treatment. Of the other xenoestrogens, bisphenol A (BPA) is one of the best-tested compounds for interactions with drugs used to treat breast cancer. It has been shown that bisphenol A could reduced therapeutic effect of active tamoxifen metabolite and cytostatics used in breast cancer treatment.

Conclusion. Confirmation in clinical trials of the results obtained *in vitro* and *in vivo* tests, would enable the creation of specific recommendations for patients undergoing breast cancer treatment, especially hormone therapy. An area requiring further research is the analysis of the effects of xenoestrogens other than phytoestrogens, e.g. metalloestrogens, on the effects of drugs used in the treatment of breast cancer.

Key words

breast cancer, estrogens, xenoestrogens, drug-xenoestrogen interaction

INTRODUCTION

Breast cancer is the most common cancer among women, affecting 2.1 million women annually, worldwide, and causing the highest number of cancer-related deaths among women [1]. In the USA in 2019, almost 267 thousand new cases of breast cancer were diagnosed, which accounted for 30% of all cancers among women [2]. In Poland in 2016, breast cancer was diagnosed in almost 19 thousand women, which constituted 23% of all diagnosed cancers in women [3]. The etiopathogenesis of breast cancer is complex and multifactorial, depending on genetic, environmental and hormonal conditions. The most frequently mentioned risk factors for breast cancer are age, obesity, genetic predisposition, previous breast cancer or non-cancerous diseases, and the activities of endogenous and exogenous estrogens, e.g. xenoestrogens found in the environment or food, which may interfere with the functioning of the endocrine system [4, 5]. It is estimated that nearly 70% of malign tumours are caused by environmental factors, whereas in breast cancer this percentage reaches 90–95% [6]. In addition, differences in the incidence of breast cancer are observed depending on the place of residence – women living in the countryside are about 1.5 times less often diagnosed with breast cancer than women living in cities [4]. It is also indicated that the higher breast cancer incidence in urban areas could be due to higher exposure to carcinogens, and may also be due to changes in lifestyle factors, including sedentary lifestyle. Thus, higher socio-economic status is associated with a higher incidence of breast cancer [7].

Estrogens (estradiol, estrone and estriol) play a key role in maintaining the hormonal homeostasis of the body through proper tissue development and the regulation of many physiological functions, including the menstrual cycle and reproduction in women [8]. In addition to their regulatory action, it is indicated that endogenous estrogens may play a role in the pathogenesis of breast cancer. Estrogens can induce the growth of cancer cells via estrogen receptors (ERs), as well as increase the rate of cell mutation (genotoxic effect) [8, 9]. Data from the literature indicate that the altered expression and function of estrogen receptors is crucial for the process of initiation and progression of hormone-dependent cancers such as breast cancer [10]. There are two types of estrogen receptors – estrogen receptor alpha (ERα,

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estrogen receptor alpha) and estrogen receptor beta (ERβ, *estrogen receptor beta*), both of which belong to the group of intracellular nuclear receptors and act as ligand-activated transcription factors. ERα and ERβ receptors may exert an opposite effect on the proliferation of mammary gland cells – ERβ receptors are indicated as proapoptotic agents, and ERα receptors as those with procancerogenic effects. According to existing knowledge, ERα plays a major role in the pathogenesis of breast cancer, while the role of ERβ in carcinogenesis is not yet fully explained [11, 12].

According to the expression of estrogen and progesterone receptors (PR, *progesterone receptor*), as well as the receptor for human epidermal growth factor type 2 (ERBB2, *erb-b2 receptor tyrosine kinase 2*; formerly HER2, *human epidermal growth factor receptor 2*), three main subtypes of breast cancer may be distinguished: ER/PR+/ERBB2-, occurring most frequently, in about 70% of cancer cases, ER/PR+ or ER/PR-/ERBB2+ (15–20% of cancers) and triple-negative cancer, without expression of the above receptors, which accounts for about 15% of cases [13].

In most patients with breast cancer, one of the basic elements of systemic treatment is preoperative or postoperative chemotherapy based on the sequential use of multi-drug regimens based on cytostatics – anthracyclines (e.g. doxorubicin, epirubicin) and taxoids (e.g. docetaxel, paclitaxel). Chemotherapy is used in patients with breast cancer – with or without steroid receptor expression. In the treatment of breast tumours with steroid receptor expression (hormone-dependent breast cancer), the basis of treatment is hormone therapy, eliminating the stimulatory effect of estrogens on the proliferation of cancer cells [14].

The role of xenoestrogens, which can mimic the action of endogenous estrogens, has been the subject of many studies in the pathogenesis of breast cancer. Definitely less is known about the impact of xenoestrogens on the effectiveness of hormone therapy used to treat breast cancer, and thus possible drug-xenostrogen interactions. It seems that these interactions may have a significant impact on the effectiveness of the therapies. Due to the widespread nature of exposure to xenoestrogens, this is a clinically important issue.

OBJECTIVE

The aim of this literature review is to summarize the current state of knowledge and present perspectives for further research on the impact of xenoestrogens on the effectiveness of drugs used in the treatment of hormone-dependent breast cancer.

MATERIALS AND METHOD

The presented review is based on a literature research performed in January 2020, using electronic medical databases PubMed, Embase and Scopus to identify studies relating to xenoestrogens in the context of interactions with drugs used in breast cancer hormone therapy. Search terms comprised of the following words: breast cancer, xenoestrogens, phytoestrogen, interaction, tamoxifen, aromatase inhibitor and their combination. Seventeen original research articles on animal and cell models published between 2002–2019, which seemed to be the most fitting in relation to this issue, were selected for review.

Drugs used in the treatment of hormone-dependent breast cancer. The main aim of hormone therapy used in patients with hormone-dependent breast cancer is to eliminate the stimulating effect of estrogens on cancer cells [13]. This effect can be achieved by using several groups of drugs: selective estrogen receptor modulators (SERMs, *selective estrogen receptor modulators*), selective estrogen receptor antagonists (SERDs, *selective estrogen receptor down-regulators*), aromatase inhibitors (AIs, *aromatase inhibitors*), or gonadoliberin analogues (aGnRH, *gonadotropin-releasing hormone analogues*).

For many years, tamoxifen has been considered the gold standard in the treatment of hormone-dependent breast cancer in both pre- and postmenopausal women. This is a selective estrogen receptor modulator which, by binding to estrogen ER on cancer cells, blocks the possibility of their stimulation by estrogens and inhibits their proliferation [15, 16]. Tamoxifen in some tissues, e.g. in the skeleton, by binding to estrogen receptors, has an agonist effect that mimics the effect of estrogens [16]. Another mechanism of action is characterized by fulvestrant, a selective estrogen receptor antagonist which, unlike tamoxifen, does not show any agonist effect. Fulvestrant leads to degradation of the estrogen receptor and enables the complete elimination of the effect of estrogens on the cell [17].

Reducing the effect of estrogens on cancer cells can also be achieved by using drugs that suppress estrogen production in the body. Gonadoliberin analogues are used in premenopausal patients whose estrogens are mainly produced in the ovaries. They block the pituitary gonadotropin secretion and inhibiting estrogen production in the ovaries [18]. In postmenopausal women, in whom peripheral tissues (adipose tissue, liver, skin) become the main source of estrogens, aromatase inhibitors – both steroidal (exemestane) and non-steroidal (letrozole, anastrozole), block the activity of aromatase and inhibit the conversion of androgens to estrogens [15].

In accordance with the recommendations of the Polish Society of Clinical Oncology and the recommendations of an international group of experts participating in the St. Gallen conference in 2019, the pharmacological treatment of hormone-dependent early breast cancer (stages I-III according to TNM classification [*tumour, node, metastasis*]), in premenopausal patients mainly includes the use of tamoxifen (routinely used at a dose of 20 mg/day) for 5–10 years. In postmenopausal women, tamoxifen, aromatase inhibitors or their sequences are used, also for a total of 5–10 years. In the case of advanced breast cancer (stage IV according to TNM classification), tamoxifen, high dose fulvestrant (500 mg *i.m.*) or combination therapy – aromatase inhibitor or fulvestrant + cyclin-dependent kinase inhibitor CDK4/6 (*cyclin-dependent kinase*), e.g. palbocyclib, are used [14, 19].

The schematic mechanism of the action of drugs used in the treatment of breast cancer is presented in Figure 1.

Xenoestrogens. Xenoestrogens are exogenous substances that interfere with the functioning of the endocrine system. As defined by the European Commission, 'it is an exogenous substance or mixture that changes the functions of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations' [20]. By interacting with estrogen receptors, xenoestrogens can act as their antagonists or agonists. They can also interfere with

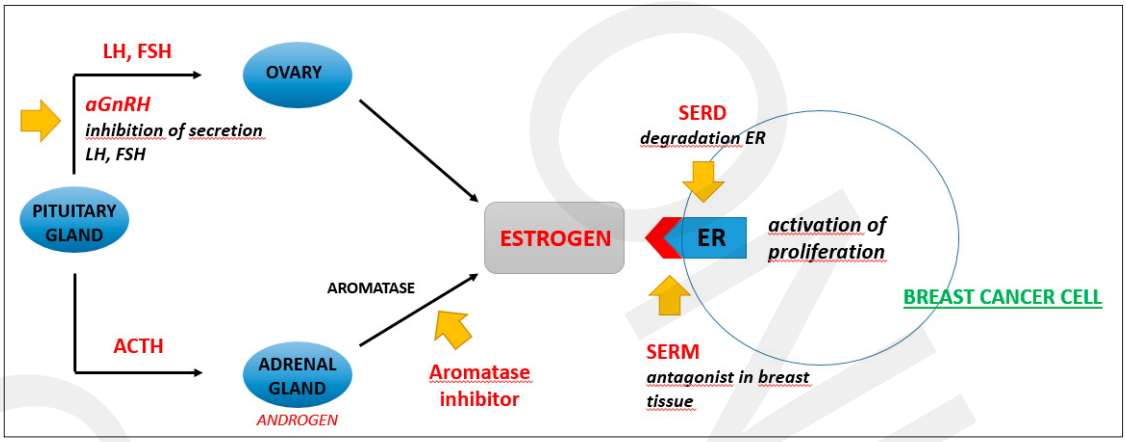

Figure 1. Mechanism of the action of drugs used in hormone therapy for breast cancer. Aromatase inhibitors and gonadoliberin analogues inhibit estrogen production in the body. SERD causes estrogen receptor degradation, while SERM in breast tissue antagonizes endogenous estrogens [13–16].
ER – estrogen receptor; FSH – follicle stimulating hormone; LH – luteinizing hormone; ACTH – adrenocorticotropic hormone; aGnRH – Gonadoliberin analogues; SERM – selective estrogen receptor modulator; SERD – a selective estrogen receptor antagonist

the synthesis and metabolism of endogenous estrogens, as well as affect the synthesis of ER. Such numerous and diverse mechanisms of xenoestrogen action are the result of the diversity of substances belonging to this group.

There are several major classes of xenoestrogens, which are show in Figure 2. This classification is based on elements of the chemical structure, which are characteristic for a group [21]. Among them, the best known group of xenoestrogens are phytoestrogens, which are a heterogeneous group of chemical compounds, currently including over 100 different substances. Based on their chemical structure, phytoestrogens are divided into isoflavones, coumestans or lignans. Their source is most often food (e.g. soy-rich foods) and dietary supplements, or over-the-counter medications used to relieve menopausal symptoms. Another group of xenoestrogens are mycoestrogens, produced by some yeasts and fungi, which are impurities in cereal products. Xenoestrogens also include metalloestrogens, including some metals – cadmium (Cd), mercury (Hg), copper (Cu), aluminum (Al), cobalt (Co), nickel (Ni), chromium (Cr) or lead (Pb). Most of them are released into the environment from industrial sources (mining, metallurgy, electroplating). Significant amounts of some metals, however, are also found in everyday life, e.g. cadmium is found in tobacco smoke, aluminum in deodorants and antiperspirants, and chromium (III) in dietary supplements used to lower blood glucose. Xenoestrogens also include

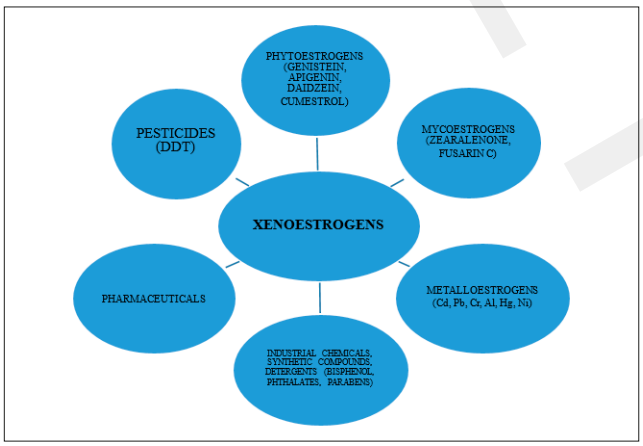

Figure 2. Classes of xenoestrogens [based on 19]

pesticides, pharmaceuticals and industrial chemicals, synthetic compounds and detergents [20, 21].

The source of xenoestrogens are various types of chemicals from industry, agriculture and technological processes, and therefore exposure to xenoestrogens may vary significantly depending on the living environment or the nature of the work performed. For example, the DDT pesticide (dichlorodiphenyltrichloroethane), commonly used in agriculture and forestry, despite being banned in the 1970s, still circulates in food chains in areas where it was previously used [22]. Exposure to pesticides occurs especially in agriculture and the chemical industry, although all persons working or living on farms may also be exposed. Occupational exposure to xenoestrogens occurs primarily in people working in the production of plastics (bisphenol A, phthalates), epoxy resins, or in the metallurgy and metal processing sectors, and industries that require welding and soldering (especially metalloestrogens – cadmium, mercury, arsenic, iron) [23].

Increasing evidence from epidemiological studies, as well as an increasingly better understanding of the mechanisms that connect toxic substances with the development of breast cancer, indicate that exposure to some environmental xenobiotics, many of which are common, in everyday products as well as their degradation products, can lead to increased risk of developing breast cancer. It is indicated that exposure to chemical compounds and radiation in the environment, both in single and combined actions or in interactions, contribute to the increasing incidence of breast cancer [24]. To better understand these relationship, in 2003 there began the BCERP (Breast Cancer and the Environment Research Programme) – a transdisciplinary study of the effects of environmental exposures on mammary development and breast cancer risk development, not only in adults, but also during the other periods of susceptibility, such as puberty [25].

The role of xenoestrogens in the pathogenesis of breast cancer has been the subject of many studies. Numerous publications confirm that many compounds commonly found in the environment can bind to estrogen receptors and thus compete or mimic the action of endogenous estrogens (e.g. stimulate the proliferation of cancer cells). This has been confirmed in *in vitro* and *in vivo* tests for

bisphenol A [26, 27, 28, 29], phthalates [30], parabens [31] and metalloestrogens [32, 33, 34], as well as mycoestrogens [35, 36]. Data on phytoestrogens, often used as a prophylaxis for breast cancer, are inconclusive [37]. In the case of isoflavone-genistein, attention is paid to its differentiated effects on MCF-7 breast cancer cells depending on the concentration used – low concentrations of genistein (10nM – 1μM) stimulate cell proliferation, while higher concentrations (> 10μM) have antiproliferative effects, which makes it difficult to unequivocally assess the appropriateness of its use in women [38].

DESCRIPTION OF THE STATE OF KNOWLEDGE

Phytoestrogens and mycoestrogens. Treatment with tamoxifen or aromatase inhibitors, due to a significant decrease in estrogen levels in the body, are often associated with uncomfortable menopause symptoms in patients, such as hot flashes, mood disorders or weight gain. One of the most common ways to deal with these symptoms is the use of dietary supplements containing plant extracts, which are a rich source of phytoestrogens, e.g. from red clover, black bedbug, hops or soybeans. Due to their vegetable, natural origin and availability without a prescription, these preparations are widely considered safe, which may result in their use by a patient without the knowledge and control of a doctor [39, 40, 41]. Phytoestrogens, in particular flavonoid genistein, are the best studied group of xenoestrogens in terms of interaction with drugs used in the treatment of hormone-dependent breast cancer. Their source can be both the above-mentioned drugs and dietary supplements intended to alleviate menopausal symptoms, as well as food (including soy, linseed, sesame, oats, clover, coffee) [42]. There are also several reports about the mycoestrogen zearalenone, which is a mycotoxin, produced by fungi of the genus *Fusarium* and occurring as a contaminant in bread and various types of cereals – corn, barley, wheat and rice [42].

One of the first reports describing the interaction between flavonoid-genistein and tamoxifen was the study by Jones et al. [43] performed on a postmenopausal breast cancer model using the T47D human breast cancer cell line. The addition of tamoxifen to a culture medium was shown to inhibit the proliferation of T47D breast cancer cells and stop the cell cycle in the G1 phase, which confirms the antitumour efficacy of the drug. The addition of low levels of genistein (<10 mM) reversed the therapeutic effect of tamoxifen [43]. Similar results were obtained by Ju et al. [44] conducting a study on ovariectomized mice implanted with estrogen-dependent breast cancer cells (MCF-7). The main parameter studied was the tumour surface at week 32 of the experiment. The mice were assigned to one of 6 groups depending on the substances used or their combination: 1) control; 2) 0.25 mg estradiol; 3) 0.25 mg estradiol + 2.5 mg tamoxifen; 4) 0.25 mg estradiol + 5 mg tamoxifen; 5) 0.25 mg estradiol + 2.5 mg tamoxifen + 1,000 ppm genistein; and 6) 0.25 mg estradiol + 5 mg tamoxifen + 1,000 ppm genistein. Estradiol and tamoxifen were administered as subcutaneous implants, while genistein (1,000 ppm per day) was added to food. It was shown that the use of tamoxifen at both doses inhibited estradiol stimulated tumour growth in mice, while this effect was inhibited in the presence of phytoestrogen, which indicates that genistein antagonizes the effect of tamoxifen [44]. Similar observations were made by Du et al. [45] examining the effect of 3 doses of genistein (250 ppm, 500 ppm and 1,000 ppm of genistein) on the effectiveness of tamoxifen in ovariectomized mice implanted with MCF-7 cells. It was shown that low doses of genistein (250 ppm and 500 ppm) significantly reduced the effect of tamoxifen, while higher doses (1,000 ppm genistein) did not affect the activity of the drug [45].

Liu et al. [46], in a mouse model, studied the effect of a diet containing high and low doses of isoflavones (genistein and daidzein) on the effectiveness of tamoxifen used in the prevention of breast cancer. The researchers showed that mice receiving a diet containing low doses of isoflavones (~211 μg/g) and tamoxifen (5 mg as a subcutaneous implant) had a significantly faster tumour growth. In addition, *in vitro* studies performed on MCF-7 cells confirmed that low doses of phytoestrogen administered together with tamoxifen promote cell proliferation. In turn, enriching the diet of mice with high doses of isoflavones (~500 μg/g), as well as adding them to the culture medium in *in vitro* tests, inhibits tumour growth in mice and MCF-7 cells in culture. The authors emphasize that the demonstrated interaction between low doses of genistein and tamoxifen may be important for patients using this drug in the treatment or prevention of breast cancer [46].

Literature data indicate that the ability of genistein to promote the proliferation of breast cancer cells is associated with its high affinity for the ERα. Seo et al. [47] evaluated the effect of genistein and apigenin (also a phytoestrogen from the flavonoid group) on breast cancer cell lines with steroid receptor expression – MCF-7 and T47D and without expression – MDA-MB-435. Both phytoestrogens have been shown to stimulate the proliferation of cells expressing estrogen receptors, which was not seen with the MDA-MB-435 cell line. Various concentrations of phytoestrogens were tested in the range from 10 nM – 10 mM, both in the presence and absence of 0.1 mM 4-hydroxy tamoxifen (4-OH-Tam, *4-hydroxytamoxifen*), the active metabolite of tamoxifen. Genistein, in addition to stimulating cell proliferation of the MCF-7 and T47D lines, additionally inhibited the antiproliferative effect of 0.1 μM 4-OH-Tam (at a concentration of 10 μM in MCF-7 cells and at concentrations from 10 nM – 10 μM in T47D cells). Apigenin only slightly inhibited 4-OH-Tam, which is probably due to its lower affinity for ERα than genistein. The authors of the study point out that the concentration of phytoestrogens achieved in the human body (from diet and/or additional supplementation) are usually in the range of 1 – 18.5 μM. Thus, these are the concentrations that can stimulate the growth of ER-positive breast cancer cells, as well as block the effects of tamoxifen. Therefore, phytoestrogens, and in particular genistein, used in the form of dietary supplements, among others for fighting hot flashes in women using tamoxifen, may be unfavourable for them, as they may reduce the effectiveness of hormone therapy [47].

Important information about the interaction of tamoxifen and phytoestrogens has been provided by a study conducted by Constantinou et al. [48] on female Sprague-Dawley rats, whose diet, depending on the study group, was enriched with tamoxifen (0.125 mg/kg diet), genistein (140 mg/kg diet), daidzein (105 mg/kg diet) or a combination of tamoxifen with each of the phytoestrogens at the aforementioned doses. Observations were made with respect to

the group in which no additional dietary modifications were introduced. After a week of using the above-mentioned diet modifications, all animals initiated a tumour process with dimethylbenzanthracene (DMBA). It was shown that in the group of females fed with tamoxifen and daidzein, the smallest incidence of cancer occurred, whereas in the group receiving tamoxifen and genistein, the incidence of cancer was higher than in the group receiving only tamoxifen (60% TAM + DAI group vs 95% control group DMBA vs 79% group TAM + GEN vs 73% group TAM; data represent the percentage of animals in which a tumour developed). It is therefore clear that some phytoestrogens, in this case genistein, can negatively affect the action of tamoxifen, while others, such as daidzein, have a synergistic effect [48]. Emodine, which is an anthraquinone classified as a phytoestrogen, also inhibits tamoxifen. In a study conducted on MCF-7 and ZR 75–1 (ER-positive and HER2 positive breast cancer cell line), the simultaneous use of emodine and endoxifen (the active metabolite of tamoxifen) weakened its therapeutic effect by increasing the expression of cyclin D1, which is a key protein that stimulates the growth of cancer tissue [49].

Considering that most of the supplements used to relieve menopausal symptoms are multi-component preparations containing a combination of several phytoestrogens, the effect of which may accumulate, van Duursen et al. [39] studied the effects of both genistein and 8-prenylnarygenin alone and 4 multi-component dietary supplements on the effectiveness of 4-hydroxy tamoxifen and letrozole. Studies have been conducted on the coculture of the MCF-7 and H295R (*human adrenal cortex cell line*) cell lines assessing tumour cell proliferation, aromatase activity and steroidogenesis, and on the BG1Luc4E2 line (*estrogen-responsive recombinant human ovarian*) to assess ERα activation. Genistein, 8-prenylnarygenin, as well as all the tested supplements containing various combinations of phytoestrogens, have been shown to activate an estrogen-dependent increase in MCF-7 cell proliferation that was not inhibited by either 4-hydroxy tamoxifen (co-administered with genistein or 8-prenylnarygenin) or by letrozole (in each combination tested – with genistein, 8-prenylnarygenin, and with each of the 4 others commercially available). It was also shown that all tested supplements and genistein increased aromatase activity, while 8-prenylnarygenin strongly inhibited its activity. Based on the results obtained, the authors recommend the avoidance of the use of dietary supplements containing phytoestrogens by patients undergoing breast cancer treatment [39].

Similarly to the studies with tamoxifen, Ju et al. [50] assessed the effect of genistein on aromatase inhibitor therapy – letrozole. In this study, ovariectomized mice were implanted with estrogen-dependent breast cancer cells (MCF-7) and randomly assigned to one of 10 groups depending on the compounds given to the mice or a combination thereof: 1) control; 2) 250 ppm genistein; 3) 500 ppm of genistein; 4) 1,000 ppm genistein; 5) 5 mg androstenedione (aromatase substrate); 6) 1 mg letrozole; 7) 5 mg androstenedione + 1 mg letrozole; 8) 5 mg androstenedione + 1 mg letrozole + 250 ppm genistein; 9) 5 mg androstenedione + 1 mg letrozole + 500 ppm genistein; 10) 5 mg androstenedione + 1 mg letrozole + 1,000 ppm genistein. Androstenedione and tamoxifen were administered as subcutaneous implants, while genistein was added to food at appropriate daily doses. The main parameter studied was the tumour area, evaluated in the 19th week of the experiment. Letrozole was shown to be effective in inhibiting tumour growth in mice; however, this effect was inhibited by the presence of genistein (at each concentration tested). Concentration dependence, however, was observed: the higher the dose of genistein used, the greater the tumour growth [50].

Different results, i.e. lack of interaction between formestane, a second generation steroid aromatase inhibitor (currently no longer used in the treatment of breast cancer) and phytoestrogens derived from the root bug extract, were shown in the animal model by Nißlein et al. [51]. The experiment was conducted on female Sprague-Dawley rats in which the tumour process was initiated by administration of DMBA. The rats were then assigned to one of 4 groups receiving: 1) 3.5 mg of formestane + black cohosh root extract; 2) 5 mg of formestane + black cohosh root extract; 3) 5 mg formestane; 4) control group not receiving additional compounds. It was shown that the use of formestane in each group was associated with significant inhibition of tumour growth, and the use of phytoestrogen did not affect its activity [51].

In 2015, the American Food and Drug Administration (FDA) approved the use of combined therapy with letrozole + palbociclib in the treatment of advanced breast cancer in postmenopausal women. The results of the PALOMA-1 clinical trial conducted in 2009–2012 on 165 patients, indicated that the use of combination therapy compared to the use of standard therapy with letrozole alone, improves progression-free survival rates by 10 months (group using combination therapy – average survival without disease progression – 20.2 months; letrozole treatment – 10.2 months). This was a significant advance in the treatment of advanced breast cancer in postmenopausal women. Warth et al. [52] examined the effect of xenoestrogens present in the diet (genistein – phytoestrogen, zearalenone – mycoestrogen) on the effectiveness of letrozole and palbociclib treatment. An *in vitro* study using the MCF-7 and T47D breast cancer cell lines showed that the combination of letrozole and palbociclib effectively inhibited tumour cell proliferation, while the addition of both genistein (1 μM) and zearalenone (100 nM) counteracted this effect. At the same time, using the Western-blot method, the combination of letrozole and palbociclib has been shown to inhibit the activity of the intracellular mTOR kinase pathway (responsible, among others, for the occurrence of treatment resistance), which is also reversed when genistein or zearalenone are added. The results obtained show how significant an effect the xenoestrogens have on the effectiveness of breast cancer treatment. The authors indicate that confirmation of the results obtained in an animal model, as well as in clinical trials, will enable the creation of specific nutritional recommendations for patients who undergo breast cancer hormone therapy [52].

Gallo et al. [53] studied the effect of soy extract, standardized on the content of genistein and daidzein, on the action of fulvestrant, which inhibited the formation of breast cancer in ovariectomized mice. Low doses of phytoestrogens – 50 mg soy extract/kg bw/day, have been shown to slightly increase the inhibitory effect of fulvestrant, while higher doses – 100 mg soy extract/kg bw/day significantly reduced the antitumour activity of the drug [53]. In contrast, the lack of interaction between fulvestrant and genistein was indicated by the results of experiments by Dess et al. [54], who showed that low doses of genistein (1μM) and zearalenone (1nM), similar to the pesticide DDT (dichlorodiphenyltrichloroethane

known for breast cancer proliferation promoting properties), increase the activity of cyclin-dependent kinase 2 (Cdk2), synthesis of cyclin D1 and hyperphosphorylation of pRbl05 (retinoblastoma protein) in MCF-7 cells. This indicates that both genistein and zearalenone stimulate proliferation, stimulating MCF-7 breast cancer cells to enter the cell cycle. The use of the anti-estrogen – fulvestrant (at a concentration of 100 nM), inhibiting the activation of Cdk2, enabled a complete reversal of this effect [54].

Multidrug resistance (MDR) is one of the main reasons for the failure of systemic cancer therapy. Various mechanisms attributed to MDR includes increased expression of drug efflux transporters, changes in tumour microenvironment and cancer stem cell regulation, increased epigenetic microRNA regulations, drug target modification, altered apoptotic signalling pathway and increased DNA repair mechanism [55]. One of the mechanisms responsible for MDR in the aspects of breast cancer development is the over-expression of proteins from the ABC (ATP-binding cassette) family of membrane transporters, which limits intracellular accumulation of cytostatic drugs and their effectiveness. ABC over-expression can be intrinsic or acquired through induction for example, by exposure to therapeutic drugs, environmental toxicants and micronutrients present in the diet. If such an induction occurs during chemotherapy, lower therapeutic response and a worse disease outcome are expected [56].

The most important transporters in breast cancer therapy are P-glycoprotein (P-gp/ABCB1), multi-drug resistance protein (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2), which are involved in the transport of, e.g. doxorubicin, epirubicin or paclitaxel. Clinical evidence points to an association between transporter expression and cancer disease prognosis. It is indicated that expression levels of BCRP predict survival after neoadjuvant chemotherapy for breast cancer, while Pgp and MRP1expression have little predictive value [57]. Rigalli et al. [58] studied the effect of genistein (at 3 concentrations – 0.1 μM, 1 μM and 10 μM) on the expression and function of ABC proteins on MCF-7 and MDA-MB-231 cell lines. Increased expression of ABCC1 (+ 121%) and ABCG2 (+ 281%) proteins in MCF-7 cells was demonstrated in the presence of 10 μM genistein, while no increase in their expression was observed at lower concentrations. In addition, in MCF-7 cells in the presence of 10 μM genistein, an increased efflux of doxorubicin (+ 55%) and mitoxantrone (+ 136%) was observed, which is associated with an increase in resistance to cytostatistics. Genistein had no effect on increasing ABCB1 protein expression, increasing the efflux of doxorubicin and mitoxantrone in MDA-MB-231 cells, while at 0.1 μM and 1 μM, it increased ABCC1 protein expression by 70% and 74%, respectively. The results indicate a risk of interaction between genistein and cytostatics used in the treatment of breast cancer, which could significantly reduce the effectiveness of chemotherapy. If genistein exerted a similar activity *in vivo*, a detrimental effect on both efficacy of chemotherapeutic drugs and on disease prognosis could be expected. These data reinforce the necessity of avoiding genistein consumption during treatment [58].

Other xenoestrogens. Of the other xenoestrogens which are not of natural origin, bisphenol A (BPA) is one of the best-tested compounds for interactions with drugs used to treat breast cancer. Bisphenol A is a synthetic diphenyl compound, with a structural similarity to a strong estrogen receptor agonist – diethylstilbestrol, which may mimic the effects of estrogen in the body. BPA is a compound widely distributed in the environment as it is a chemical raw material used in the production of plastics and epoxy resins [59]. Hence, the main source of BPA exposure are plastic containers for food and drinks, dental materials, protective coatings, and thermal paper. BPA is a compound with the ability to accumulate in tissues, and its presence has been detected in healthy people, including in urine and blood serum samples [59].

Goodson et al. [60] showed that the exposure of mammary epithelial cells (HRBEC – high-risk donor breast epithelial cell) obtained from donors (at high risk of developing breast cancer) to detectable levels of bisphenol A in human blood 100 pM – 100 nM BPA), results in a change in the expression of genes associated with the activation of the mTOR pathway, which increases the survival of cancer cells [60]. Another issue explored by this group of researchers was the effect of bisphenol A on the therapeutic effectiveness of one of the main active tamoxifen metabolites – 4-hydroxy tamoxifen. It was shown that with the simultaneous use of 4-hydroxy tamoxifen (10 μM) and bisphenol A (100 nM), the therapeutic effect of 4-hydroxy tamoxifen is reduced, measured as the percentage of cells undergoing apoptosis – both breast cancer cell lines (T47D, SKBR3) and HRBEC. This effect was even greater the higher the BPA concentration – only 50% of the cells underwent apoptosis at a BPA concentration of 100 nM [61].

LaPensee et al. [62] assessed whether bisphenol A affects the action of commonly used cytostatics – doxorubicin, cisplatin and vinblastine, and the mechanism of possible interactions. To this end, *in vitro* tests were performed on both estrogen-sensitive breast cancer cells (T47D) and estrogen-insensitive breast cancer cells (MDA-MB-468). Cytotoxicity of 3 different concentrations of doxorubicin (5 ng/mL, 25 ng/mL, 124 ng/mL), cisplatin (100 ng mL, 200 ng/mL, 400 ng/mL) and vinblastine (1 ng/mL, 5 ng/mL, 25 ng/mL) were assessed in the absence and presence of bisphenol A (at 1 nM). All cytostatics at each concentration were shown to be cytotoxic in the absence of BPA on both cancer cell lines. The addition of BPA antagonized this effect. It was also shown that this effect is not associated with BPA via estrogen receptors, but is the result of the increased expression of antiapoptotic proteins (Bcl-2 and Bcl-xL). Thus, the authors confirmed that bisphenol A at nanomolar doses occurring in humans as a result of environmental exposure, may reduce the effectiveness of chemotherapy, which should be taken into account when using anti-cancer therapy [62].

Research by Osuna et al. [63] published in 2017, suggests that another synthetic xenoestrogen – methylparaben, contributes to the occurrence of chemo-resistance to drugs used in the treatment of breast cancer (tamoxifen, fulvestrant). This may be due to the direct stimulating effect of methylparaben on tumour-initiating cells (TICs), as well as by modulating the activity of stem cells that remain resistant to antiestrogens, by increasing the expression of the NANOG protein, which promotes stem cell differentiation. In a study performed on the MCF-7 cell line, it was shown that neither tamoxifen nor fulvestrant block the effects of methylparaben [63].

Table 1 summarizes the interaction studies of xenoestrogens with substances used in the treatment of hormone-dependent breast cancers in *in vivo* and *in vitro* tests.

Table 1. Summary of interaction studies of xenoestrogens with substances used in the treatment of hormone-dependent breast cancer in *in vivo* and *in vitro* tests

Author/ Lear	Cell line/Animal	Xenoestrogen	Drug	Results
SERM – tamoxifen or active metabolite of tamoxifen (4-hydroxytamoxifen or endoxifen).				
Jones et al., 2002 [37]	T47D	GEN <10μM	TAM	GEN reversed the inhibitory effects of tamoxifen on both proliferation and G1 arrest.
Ju et al., 2002 [38]	MCF-7 implanted in ovariectomized athymic mice	GEN 1,000 ppm	TAM	GEN negated the inhibitory effect of TAM; increased expression of estrogen-responsive genes (e.g. pS2, PR and cyclin D1).
Liu et al., 2005 [40]	MCF-7; mouse mammary tumour cell line	diet with low doses of isoflavones (~ 211 μg/g); diet with high doses of isoflavones (~ 500 μg/g)	TAM	Low doses of GEN, co-administered with TAM, promote cell proliferation; in contrast TAM with high doses of GEN that are growth inhibitory.
Constantinou et al., 2005 [42]	Sprague-Dawley rats given DMBA	GEN (140 mg/kg diet), DAI (105 mg/kg diet) as a diet component	TAM	GEN and TAM combination had increased tumour multiplicity, compared with TAM alone; DAI with TAM had reduced tumour multiplicity.
Seo et al., 2006 [41]	MCF-7, T47D, MDA-MB-435	GEN, API in concentration 10nM -10μM	4-OH-TAM	GEN antagonizes the anti-proliferative effect of 4-OH-TAM; API even at 10μM appeared to only have a moderate effect on blocking TAM effect.
Goodson et al., 2011 [51]	HRBEC, MCF-7, T47D, SKBR3	BPA (100pM to 100nM), mePB (10nM to 1μM)	4-OH-TAM	HRBECs pretreated with BPA, or mePB surmounted antiestrogenic effects of tamoxifen showing dose-dependent apoptosis evasion and induction of cell cycling.
Du et al., 2012 [39]	MCF-7 implanted in ovariectomized athymic mice	GEN 250 ppm, 500 ppm, 1000 ppm	TAM	Inhibitory effect of TAM was significantly negated by the low doses of GEN (250 and 500 ppm), whereas the 1,000 ppm. GEN did not have the same effect.
Kim et al., 2019 [43]	MCF-7, T47D, ZR-75–1, BT474	Emodin 15, 30, 60 μM	Endoxifen	Combination emodin and endoxifen attenuated treatment effect via cyclin D1 and pERK up-regulation in ER(+) breast cancer cell lines.
Aromatase inhibitors – steroidal (formestane) and non-steroidal (letrozole). Combination AI with CDK4/6 inhibitor – palbociclib.				
Niβlein et al., 2007 [45]	Sprague-Dawley rats given DMBA	iCR – 60 mg herbal substances per kg body weight	Formestane	iCR did not antagonize or diminish the antitumoural effects of formestane
Ju et al, 2008 [44]	MCF-7 implanted in ovariectomized athymic mice	GEN 250 ppm, 500 ppm, 1000 ppm	LET	GEN reversed the inhibitory effect of LET in a dose-dependent manner.
van Duursen et al., 2013 [33]	MCF-7/H295R, BG1Luc4E2	GEN, 8PN, 4 commercially available menopausal suplements	4-OH-TAM, LET	GEN, 8PN and 4 supplements all induced ER-dependent tumour cell proliferation, which could not be prevented by LET and 4OH-TAM
Warth et al., 2018 [46]	MCF-7, T47D	GEN 1μM, ZEA 100 nM	PAL+LET	GEN and ZEA reversed the inhibitory effect of PAL+LET combination on cancer cells proliferation.
SERD – fulvestrant				
Dees et al., 1997 [48]	MCF-7	GEN 0,1μM, ZEA 10 nM	FUL (ICI 182 780)	FUL suppressed dietary estrogen-mediated activation of Cdk2.
Gallo et al., 2007 [47]	MCF-7 implanted in ovariectomized athymic mice	SSE containing GEN, DAI at 50 or 100 mg/kg per day	FUL (ICI 182 780)	Concomitant administration of 50 mg/kg per day SSE slightly potentiated the inhibitory activity of FUL, while at 100 mg/kg per day, SSE partially negated FUL activity.
Osuna et al., 2017 [54]	MCF-7, MDA-MB-231	mePB 10 nM	TAM, FUL	mePB increases breast cancer tumour proliferation through enhanced TIC activity and regulates stem cell genes (inc. NANOG); TAM and FUL do not block these effects.
Cytostatic agents e.g. doxorubicin, cisplatin				
LaPensee et al., 2009 [53]	T47D, MDA-MB-468	BPA 1nM	DOX, CIS, VIN	BPA antagonizes the cytotoxicity of chemotherapeutic drugs in both ER-positive and ER-negative breast cancer cells
Rigalli et al., 2016 [49]	MCF-7, MDA-MB-231	GEN 0,1μM, 1μM, 10μM	DOX, MXR	In MCF-7 cells, GNT (10 μM, increased DOX efflux (+55%) and MXR efflux (+136%).

T47D, MCF-7 – ER-positive breast cancer cell lines; MDA-MB-435 – ER-negative breast cancer cell lines; H295R – human adrenal cortex cell line; BG1Luc4E2 – estrogen-responsive recombinant human ovarian cell line; HRBEC – high-risk donor breast epithelial cells; DMBA – dimethylbenzanthracene; pERK – phosphorylated extracellular signal-regulated kinase; TIC – tumour initiating cells; GEN – genistein; API – apigenin; ZEA – zearalenone; DAI – daidzein; 8-PN – 8-prenylnaringenin; iCR – isopropanolic extract of black cohosh; SSE – standarized soy extract; mePB – methylparaben; BPA – bisphenol A; TAM – tamoxifen; 4-OH-TAM – 4-hydroxytamoxifen; LET – letrozole; PAL – palbociclib; FUL – fulvestrant; endoxifen – active metabolite of TAM; DOX – doxorubicin, MXR – mitoxantrone, CIS – cisplatin, VIN – vinblastine

CONCLUSIONS

Given our widespread exposure to xenoestrogens, as well as the steady increase in the incidence of breast cancer, examination of the impact of these endocrine active compounds found in the human environment on the effectiveness of therapies used to treat hormone-dependent breast cancer is becoming an important clinical and social issue. As shown in this literature review, most research has focused on phytoestrogens, due to their frequent use, including their use in alleviating the adverse effects of hormone therapy. Analyzing the current state of knowledge, it seems that their intake should be avoided during conventional anti-cancer treatment, due to the possibility of reducing the effectiveness of therapy and thus increasing the risk of disease progression. Confirmation in clinical trials of the results obtained *in vitro* and *in vivo* tests, would enable the creation of specific nutritional recommendations for patients undergoing breast cancer hormone therapy, which may improve the effectiveness of treatment.

An area requiring further research is analysis of the effects of xenoestrogens other than phytoestrogens, e.g. metalloestrogens, on the effects of drugs used in the treatment of breast cancer. Exposure to metalloestrogens is common (e.g. cadmium – smoking, chromium (III) – dietary supplements, or aluminum – the use of deodorants and antiperspirants), and their carcinogenic potential has been proven in many *in vitro* tests, which suggests that, like phytoestrogens, they may affect the effectiveness of the therapies used in the treatment of hormone-dependent breast cancer.

Another interesting and important aspect for conducting further research is to examine the potential relationship between the exposure to environmental xenoestrogens with confirmed carcinogenic potential, e.g. pesticides, industrial chemicals or metalloestrogens, and the effectiveness of treatment of hormone-dependent breast cancer. Due to the differences in the incidence of breast cancer depending on the place of residence, as well as the varied exposure to environmental xenoestrogens depending on the living environment, this seems to be a clinically relevant issue.

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