REVIEW ARTICLE
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ENDOCRINE DISRUPTORS AND THEIR INFLUENCE IN THE ORIGIN OF BREAST NEOPLASM AND OTHER BREAST PATHOLOGIES

Disruptores endócrinos e o seu papel na gênese das neoplasias e de outras patologias das mamas

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ABSTRACT

A higher occurrence of early breast cancer in women has created the need to identify possible etiologic agents characterized as direct co-responsible. The motivation for this review is the relevance of detecting potential endocrine disruptors responsible for harmful effects on breast tissue and, consequently, its damage.

KEYWORDS: Breast; breast cancer; breast neoplasms.

RESUMO

Uma maior ocorrência no surgimento precoce das neoplasias das mamas em mulheres tem gerado a necessidade da descoberta dos possíveis agentes etiológicos caracterizados como corresponsáveis diretos. A relevância da detecção dos possíveis disruptores endócrinos responsáveis por exercer efeitos danosos nos tecidos mamários e, consequentemente, o seu comprometimento é a motivação da presente revisão.

PALAVRAS-CHAVE: Mama; câncer de mama; neoplasias da mama.

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INTRODUCTION

In recent decades, a higher incidence of hormone-dependent neoplasms has been observed in body parts such as breasts, endometrium, ovaries, testicles, prostate, and thyroid. Despite the recent increase in implementation of methods for early diagnosis, numerous other possible etiologic factors — such as dietary habits and use of pharmaceutical or chemical drugs — may share the responsibility for the greater occurrence of these neoplasms.

This review proposes an analysis of possible deleterious actions of carcinogenic agents — known as endocrine disruptors (ED) — that could be involved in the onset of various pathologies and breast neoplasms, and possibly implicated in these areas in several animal species.

Among many agents considered to be ED, we have:

1. Bisphenols (Figure 1): constitute a wide range of substances. Their first synthetization was in 1891, but in 1936, evidence of estrogenic activity[1] was found in Bisphenol A (BPA). Their annual production continually expands due to large consumption and diverse use in products like toys, plastics, food packaging, and in epoxy resins. BPA can be ingested or act via transdermal or sublingual routes and undergoes fast liver metabolization[2-4]. Because it is lipophilic, it accumulates in fat tissues. Since 1950, it is possible to polymerize BPA to produce polycarbonate plastic, which is very flexible, lightweight, transparent, and resistant to heat and various chemicals. Five other bisphenols are in current use: bisphenol B (BPB), bisphenol F (BPF), bisphenol S (BPS), bisphenol AF (BPAF) and tetrabromobisphenol A (TBBPA);
2. Phthalates (Figure 2): phthalates and phthalate esters are also commonly used in the plastic and toys industries, in cosmetics, and in medical tubing manufacturing. Because of its broad dissemination in the world, this substance is also used by the food industry in products such as fruit juices, sports drinks, food supplements, and frozen food such as ice cream[5];
3. Atrazine (ATR) (Figure 3): atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) is widely used as an herbicide to control weeds in crops of corn, soy, and sugar cane. It remains active for a long time, and, consequently, contaminates water tables and is responsible for abnormalities in many aquatic organisms, according to Solomon et al.[6];
4. Polychlorinated biphenyls and polybrominated biphenyl esters: this group of aromatic chemical substances has a

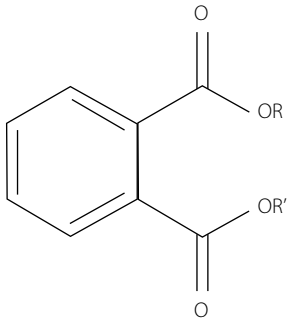
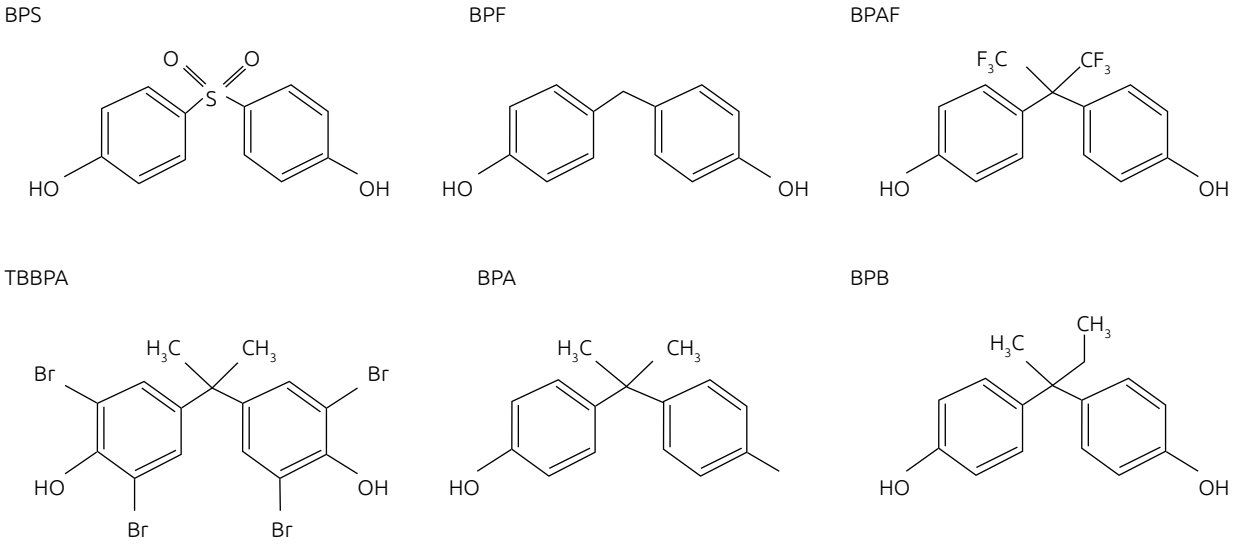


Figure 2. Structural formula of phthalates.



BPS: bisphenol S; BPF: bisphenol F; BPAF: bisphenol AF; TBBPA: tetrabromobisphenol A; BPA: bisphenol A; BPB: bisphenol B.

Figure 1. Structural formulas of bisphenols.

phenolic aromatic ring with chlorine or bromine radicals and is highly toxic. The synthetization of these products started in the late 1920's, but some of them were banned in 1979 for their toxicity. However, due to their multiplicity, others have been used in the plastic, rubber, adhesive, dye, and resin industries. Some of these products have thyroidogenic, estrogenic, or antiandrogenic activities[7,8]. Polybrominated diphenyl ethers (PBDE) used to be used as flame retardants in upholstered furniture, mattresses, and even in clothing production[9];

5. Dichlorodiphenyltrichloroethane (DDT), dichlorodiphenyldichloroethylene (DDE) and dichlorodiphenyldichloroethane (DDD): DDT is an insecticide with long average life and lipophilic activity, which unfortunately has become a major environmental contaminant. The United States banned DDT in 1972, despite its benefits in reducing malaria and typhus[10,11]. DDE and DDD are metabolites of DDT, the latter being associated with the origin of endocrine diseases like diabetes mellitus type 2, and endometrial, pancreatic and breast cancers[12-14].
6. Diethylstilbestrol (Figure 4): powerful nonsteroidal estrogen synthesized in 1938 and formerly used in the United States for the treatment of threatened abortion and its possible complications[12]. Its initial dose was 5 mg/day, being progressively increased to 125 mg/day until the total dose of 3,650 to 4,000 mg.

However, in 1953, a study by Dieckman et al. proved its ineffectiveness for this indication[13]. In 1971, a work by Herbst et al. examined young women whose mothers had used this substance during their pregnancies and described a higher occurrence of vaginal adenosis-adenocarcinoma among them. In 1976, the same author reported other abnormalities in the female genital apparatus[14,15]. Also, Harris and Warring (2012) and Troisi (2014) found a higher incidence of genital abnormalities such as cryptorchidism in boys whose mothers had used the same substance. Daughters of these women also presented an anomaly described as T-shaped uterus and more occurrence of hormone-dependent tumors[16,17].

ONCOGENIC ACTIONS OF BREAST DISRUPTORS

Component of mammal reproductive system responsible for lactation, the mammary gland is particularly sensitive to ED as it involves systems of growth, differentiation, secretory activities and also of regression, all under the influence of hormones and numerous growth factors. As a result, the breast tissue is quite influenceable in very distinctive ways during three phases of life: puberty, pregnancy, and breastfeeding.

In the course of a pregnancy, when the breast buds receive a signal to form ducts and their extension to the underlying fat tissue, many ED can change the formation of mammary structures. Also, ED actions are deleterious to breasts in puberty since they grow exponentially by proliferating when a fast division of terminal mammary ducts and of the breast bud occurs.

Higher risk of breast neoplasms has been correlated with the early start of puberty and menarche, menopause at a late age, nulliparity, late first pregnancy, and obesity in pre-menopause.

There is a large number of chemical substances associated with the development and growth of breast tissue that pose a higher risk of breast neoplasms due to their actions.

The carcinogenicity of various substances

A study conducted with rodents in 1982 by the *United States National Toxicology Program* established that a BPA dose of 75 to 150 mg/kg weight/day is enough to exert carcinogenic activity. For its weak evidence, this study was questioned as to numerous factors, such as the non-inclusion and evaluation of these animals in their perinatal period[18]. In their studies — which included the periods of gestation and lactation with oral doses of 10 to 250 ug/kg weight/day —, Timms et al. (2005) and Moral et al. (2008) observed proliferative lesions in the mammary ductal epithelium and also prostatic squamous metaplasia in newborn

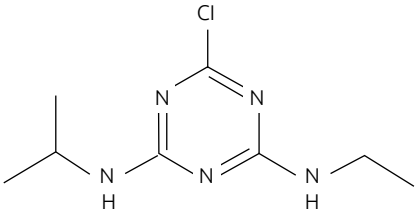


Figure 3. Structural formula of atrazine.

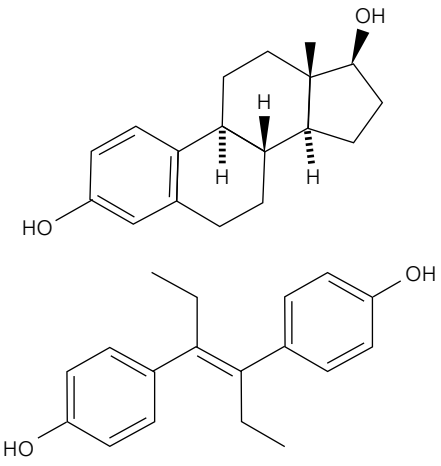


Figure 4. Structural formulas of estradiol and diethylstilbestrol.

rats, lesions susceptible to neoplasms[19,20]. Posterior studies by Jenkins et al. (2009) and Prins et al. (2011) showed that these agents generated an early condition for the appearance of breast and prostatic intraepithelial neoplasms in these animals[21,22].

However, these studies, which consisted in the exposure of animals to BPA in specific periods of their lives, had some deficiencies in design, such as the small sample, failure in time of use and/or additional treatments they underwent. These limitations prevented a definitive conclusion about their oncogenic potential.

Despite a large number of existing chemical substances with activities that mimic sex hormones, organochlorines are the main responsible for deleterious effects in various locations. Among them, we have 1,1,1-trichloro-2,2-bis (p- chlorophenyl)-ethane (DDT) and its isomer, p'-DDT, both of which have estrogenic properties; 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene with antiandrogenic action; 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), considered an antiestrogenic; and polychlorinated biphenyl (PCB) and its congeners, which can have estrogenic or antiestrogenic activities[23-26].

DIOXINS

There are more than 400 types of dioxins, but out of them, 30 are toxic to humans, TCDD being the most toxic. TCDD is a substance with large lipophilic capacity and a long average lifespan (7 to 11 years) that has been used as herbicide and pesticide. For its antiestrogenic capacity, TCDD reduces plasma levels of estradiol and alters breast development. Studies in humans conducted in Belgium by Den Hond et al. (2002) and in the Netherlands by Leijs et al. (2008) assessed children living in areas contaminated by dioxin who showed evident signs of delay in breast development[27,28].

Another historical incident occurred in Seveso, Italy (1976), when a large amount of TCDD was released in the environment.

Subsequent studies — which monitored all people contaminated in neighboring areas, dividing them according to degree of contamination — allowed the analysis of a possible higher incidence of neoplasms throughout the years.

According to Bertazzi et al. (1989 and 1997), the 10 and 15-year follow-up analyses of this population did not show an increase in the occurrence of neoplasms or higher mortality[29,30]. On the other hand, a 20-year follow-up analysis demonstrated discrete higher incidence of neoplasms in the population group that suffered greater contamination[31]. Warner et al. (2002) reassessed the same population assessed by Seveso for the *Women's Health Study* aiming to explore the possibility of higher incidence of breast neoplasms. Subjects exposed to the dioxin incident early in childhood and who had plasma level 10 times above the acceptable showed a twice higher incidence of breast neoplasms. This group was not yet between 40 and 55 years of age, stage of life in which this neoplasm is more common[32].

Another epidemiological study carried out by Revich et al. in the Chepayevsk region of Russia, where dioxin contamination also occurred, revealed a higher incidence of breast cancer among women living close to contamination area[33].

Also, in several studies with animals — rodents exposed to dioxin, for example — there was a larger number of alterations in breast development, such as high deficiency in the development of lobules and their size[34,35]. Other studies with rats exposed to dioxin in the prenatal period, such as those by Brown et al. and Desaulniers et al., showed more cases of adenocarcinomas in the breasts[36,37].

Dichlorodiphenyltrichloroethane, dichlorodiphenyldichloroethylene, and dichlorodiphenyldichloroethane

Studies in humans revealed that DDT and DDE can reduce the ability to breastfeed in women, according to previous works by Rogan et al. and Karmaus et al.[38,39]. References and analyses of the *National Toxicology Program* showed that DDE acts similarly to estrogens or antiandrogens. Thus, it can interfere with hormonal levels during lactation[11].

For years, there has been a huge concern about these substances known as ED, and many studies about them have been conducted. They can exist in the environment or be manufactured, and even trigger breast cancer. As most of these studies are considered case-control, results are disparate, and it is difficult to draw a statistically significant conclusion. Another obstacle is the possible association of existing substances or contaminants that could be acting in a nefarious and simultaneous way, which could make it hard to reach an accurate conclusion.

Before 1995, seven case-control studies were produced and directed to analyze the concentration of different organochlorine substances in tissues or serum.

Wasserman et al. (1976) conducted the first study, which examined the presence of DDT or PCB metabolites in fragments of breast tissue fixed in formalin, collected from nine patients with breast neoplasms and five women of a control group. Lipids in breast fragments with neoplasia had higher concentrations of PCB than those in breast tissue of women from the control group. However, the concentration of the bigger DDT metabolite — p,p'-DDE — was significantly higher in the control group[40].

The second and third studies, by Unger et al. (1984) and Mussalo-Rauhamaa et al. (1990), analyzed the presence of DDE or DDT metabolites in a series of fragments of breast tissues from patients with neoplasms (newly dead) and a normal control group. None of them had different concentrations, only an increased level of beta-hexachlorocyclohexane. These results did not allow conclusions, since the tissue fragments used came from deceased women[41,42].

The fourth study, by Falck et al. (1992), investigated the presence of seven organochlorine substances in breast tissue from

women with breast neoplasms and a control group. The tissue from women with cancer had high levels of DDE and PCB, but after classifying participants by age group and tobacco use, the values were not statistically significant[43].

A fifth study, by Dewailly et al. (1994), examined the presence of positive or negative receptors for estrogen in neoplastic breast tissues and found a greater presence of PCB or DDE in distinct groups, but the number of samples used for this study was small, the reason inaccurate conclusion[44].

In 1993, Wolff et al. (sixth study) observed a cohort of 14,290 patients living in the New York City area who had been subjected to a screening mammogram between 1985 and 1991. Among them, 58 were diagnosed with breast cancer. Their mean age was 51 years, and 80% of them were white-skinned women, with high serum levels of PCB and DDE[45].

In 1994, Kriener et al. conducted another important study (seventh) with a group of women from California monitored from 1964 to 1971. They selected 150 patients who developed breast cancer and 150 for the control group. Three racial groups were assessed: Asian, black, and white women with similar ages. When the racial groups were examined separately, white and black women had higher serum concentrations of DDE compared to the control group, while Asian women had lower levels. Multivariate control studies aimed at monitoring body mass index, age at menarche, pregnancies, and menopausal status were used to evaluate estimated risks. After PCB levels were checked, Asian and white women showed lower values when compared to their control groups. Through statistical analysis and based on odds ratio (OR), the conclusion of the study was that there is no association between serum concentrations of organochlorines and increased risk for breast cancer, and that serum levels differ according to geographical location[46].

In the study by Wolff et al., serum levels of DDE were 7.7 ng/mL, when compared with the control group. In Krieger et al., the levels were 35 ng/mL for white women, 43.4 ng/mL for black women, and 50.8 ng/mL for Asian women. Black and Asian women had higher serum concentrations as compared to white women[45,46].

Studies prior to 1995 did not draw any conclusions on the possible association of levels of DDT, its metabolites, and PCB with greater risk of breast cancer. However, other important studies have been produced since then, mostly case-controls, to analyze the relationship between DDT, its metabolites or PCB, and adipose tissue or serum levels of these patients.

The study by van't Veer et al. evaluated DDE levels in relation to breast neoplasms in tissue samples from patients living in five European countries. The group consisted of post-menopausal women and included 265 people with neoplasms and 341 controls. Using logistic regression and adjusting for age, sex, body mass index, alcohol consumption, and age at the end of first pregnancy, the researchers observed that DDE levels varied according to the country where the patients lived, but that levels below 1.9 μg/g pose no risk of neoplasm. These results allowed to conclude that the level of exposure to DDE does not increase the risk of breast cancer[47].

Two other studies, by Liljegren et al. in Sweden and Guttes et al. in Germany, analyzed the presence of DDE and PCB in adipose tissue of breasts with carcinoma. After multiple analyses, they concluded that there was no correlation between the concentration of these substances and breast carcinoma in humans[48,49].

In 1996, a study by Sutherland et al. researched several compounds (*Charleston Heart Study*) in a cohort of 405 white and black women and detected DDE serum levels of 32.0 ng/mL between 1974 and 1975, similar to the findings by Krieger et al.[46]. During the follow-up, done until 1994, 20 women developed breast carcinoma, and, in regression models and analysis of other variables, no evidence of a greater occurrence of breast neoplasm with the increased DDE concentrations was found[50].

Hunter et al., analyzed a cohort of 12 thousand female nurses in the Nurses Health Study, with follow-up since 1976, to evaluate DDE and PCB blood levels in 240 women with breast cancer and in an equal number of women in a control group. Mean value of DDE was 6.01 ng/mL (with 6.97 ng/mL in the control group), while PCB were 5.08 and 5.16 ng/mL. After several multivariate adjustments and comparisons, the findings showed no association between higher plasma levels of organochlorines and increased risk of breast cancer[51].

Outside the Europe-United States axis, Lopez-Carrillo et al. (1997) investigated a Mexican population where DDT was used more often, including for malaria control. The group consisted of 141 women with breast neoplasms and a control group of the same size. The results were similar, with DDE serum levels of 4.75 ng/mL (4.07 ng/mL in the control group), and no other statistically significant result[52].

A study carried out in Copenhagen by Hoyer et al. (Copenhagen City Heart Study) with a group of 7,712 women who had their sera stored, followed by another from the Danish Cancer Registry, identified 240 women with breast cancer and 477 for control. Eighteen different pesticides and their metabolites were identified, as well as 28 different types of PCB. Through statistical tests and logistic regression analyses, no association with DDT and its isomers or any other PCB congener was found. Among many compounds studied, only dieldrin could be listed as possibly associated with breast cancer, with OR of 1.96 and 2.05[53].

Subsequent studies have shown, in an inconsistent way, that the use of DDT and/or its metabolites could induce a higher incidence of breast cancer. A case-control study performed by Cohn et al. specifically demonstrated that a higher incidence of these neoplasms depends on the age of exposure to DDT and DDE. High serum levels of p,p'-DDT correlated with age,

especially for those born before 1931, showed an increase in incidence up to five times in women subjected to such exposure before the age of 14[54].

Boada et al. carried out another study in the Gran Canary Islands (Spain), which evaluated the exposure to multiple organochlorine pesticides in humans and their diverse influences. After analysis of multiple variables, serum levels of DDE, DDD, and aldrin — Hexachlorocyclopentadiene, an insecticide — were found to be very high in women with breast cancer, when compared to a group of healthy women[55].

White et al. studied a group of women for the project Long Island Breast Cancer Study, where an acute exposure to DDT occurred, as to the presence of estrogen and progesterone receptors in women exposed to it under the age of 20. They observed an increased risk of breast neoplasm, in relation to a control group that did not suffer such contamination[56].

In a large meta-analysis, Ingber et al. demonstrated widely conflicting data and a diversity of results as to the association of DDT and DDE levels with the occurrence of breast neoplasms. These studies have a broad variety of data, such as age, menopausal status, study designs, and variables considerations that make it difficult to reach conclusions on this possible association[57].

BISPHENOLS

BPA is similar to estradiol and joins the alpha estrogen receptor with weak activity, but it has a strong affinity to the gamma receiver and G protein, being able to induce the proliferation of breast epithelial carcinoma cells through stimulation of the alpha estrogen receptor[58-60]. Many *in-vitro* studies and other methodologies conducted with rodents have shown that BPA can change breast development during its growth as well as induce a greater risk of growing tumors. Studies by Markey et al., Munoz de Toro et al., and Acevedo et al. showed that exposure to BPA at low doses in fetal and perinatal periods can stimulate, during puberty, the onset of pre-neoplastic lesions of various hyperplasia degrees; and also, when administered in doses higher than 2.5 μg of BPA/kg, it induces ductal adenocarcinomas[61-64]. An incident in Michigan, United States, in 1973, led to food contamination by polybrominated biphenyl, impacting 3,653 individuals. Due to the possible risk of death, they were monitored until 1991. Henderson et al. analyzed the occurrence of breast cancer in this group and found that subjects with PBB concentrations beyond 2 ug of BPA/kg had higher risk of developing these neoplasms, which was the case for 20 women diagnosed with breast cancer[65].

PHTHALATES

Wolff et al. conducted a study with 1,200 pre-pubescent girls in 2014 and observed a delay in pubertal and pubic hair development in those presenting urinary levels of phthalates with high molecular weight. The substance was considered responsible for the delay due to its antiandrogenic properties. In the same study, breast development was also late in girls with high urinary concentrations of phthalates[66].

A study by Lopez-Carrillo et al. performed in northern Mexico examined the association between urinary concentrations of phthalates and breast cancer. Phthalates were detected in 82% of women, and the concentration of monoethyl phthalate (MEP) was higher in patients with breast cancer than in control patients. As a conclusion, this exposure would increase the risk of neoplasm in 2.5 times as related to the control group[67].

Studies with the use of dibutyl phthalate (DBP) demonstrated induction of reproductive toxicity in rodents due to the weak union to estrogen receptors. Such exposure in pregnant rodents would be enough to induce, via lactation, a hypoplastic development of mammary alveoli in animals that had received DBP[68].

ATRAZINE

Epidemiological studies have showed little to no association between exposure to atrazine (ATR) in agriculture and higher occurrence of breast cancer. In 1997, a study carried out in Kentucky, United States, showed that the contamination of surface waters by ATR in 1991 and 1992 significantly increased the occurrence of breast cancer in women exposed. Later, in 1993 and 1994, when, in addition to surface waters, waters of greater depth were also analyzed, this association was not observed[69,70].

Muir et al. observed a positive association between the use of ATR and a higher incidence of breast cancer after a population study conducted in Lincolnshire and Leicestershire counties, in England, from 1989 to 1991, when pesticides were applied in urban and rural regions[71].

All these studies have limitations and do not seem to suggest that the risk increases after exposure to ATR. Several studies with rodents showed that the impact of the early use of ATR can change the development of mammary glands and reduce their growth when pregnant rats and their offspring are exposed to the substance.

Although ATR is not classified as a directly carcinogenic substance, its chronic use can increase the incidence of mammary adenocarcinoma in Sprague-Dawley female rats and of mammary hyperplasia in male rats when administered in high doses[72].

DIETHYLSTILBESTROL

Diethylstilbestrol (DES), a nonsteroidal estrogen previously used for the treatment of threatened abortion doses varying from 5 to 125 mg/day was proven to induce different anomalies throughout the years. In 1971, Herbst et al. revealed that the substance was responsible for inducing the emergence of vaginal neoplasms, such as adenosis or clear-cell adenocarcinoma of the vagina in

young women whose mothers had used DES when pregnant[15]. Harris and Waring (2012), and Troisi (2013) assessed the role of DES in triggering other anomalies such as cryptorchidism in boys, uterine abnormalities known as T-shaped uterus, and hormone-dependent neoplasms[17,18].

Studies in animals have shown that DES can induce breast abnormalities such as increased growth when pregnant or nursing animals received high doses of the substance[73]. When exposure to DES occurred in the prenatal period, the risk of developing breast tumors increased due to a significant rise in proteins like EZH2 (enhancer of zeste homolog 2- induction of methylation of histone) or histone methyltransferase, which are linked to the origin of breast cancer[74].

PERFLUOROOCTANOIC ACID

A surfactant substance chemically used as grease and water cleaner, insect repellent, or firefighting foam. It is also used in dental products or food packaging, and its average lifespan is 16 to 22 days in rats and 2 to 4 years in humans. When combined with estradiol, the perfluorooctanoic acid (PFOA) has estrogenic and antiestrogenic properties *in vitro*[75].

Due to these properties, PFOA was correlated with delayed pubertal development and increased risk of breast cancer growth[76].

A study from the Breast Cancer and Environment Research Program found a direct connection between PFOA serum levels and breastfeeding received by young girls from 6 to 8 years of age. A highly significant relationship between water sources was also found in areas of the north of Kentucky and previous lactation periods, which could promote delay in breast development during the pubertal stage[73].

Also, numerous studies with animals showed a direct relation between PFOA levels and changes in breasts development and function. Exposure to PFOA during pregnancy may delay the epithelial development of mammary glands and even increase the mortality of newborns. These breast changes can increase mammary hyperplasia risk with elevation in stroma density. These conditional factors can result in higher risk of breast cancer[77].

ENDOGENOUS AND EXOGENOUS STEROID HORMONES

The use of steroid hormones — either as hormone replacement therapy or contraceptive pills — has always merited continuous observation and analysis as to their possible deleterious effects. Ever since these numerous exogenous therapies started being administered, different tissues have shown varying degrees of responses, as they suffer great variability due to the cyclic alternation provoked by the endogenous production of various hormones. The possible time of action varies widely and depends on many acting factors such as dose, growth factors involved, and type of hormone.

The various hormone actions in the breasts differ from those in the uterus and endometrium. Endogenous estrogens cause cell proliferation in the mammary gland, and under the action of progesterone in the second phase of the cycle, maturation effects and structural changes in the glands occur.

Different studies have analyzed the use of hormone replacement therapy. The Nurse Health Study showed that the relative risk of breast cancer is 1.3 for those who use only estrogen and 1.4 for those who use estrogen combined with progestogens[78].

In 2002, the Women Health Initiative (WHI) analyzed the risks posed by hormone therapy during menopause in a large random group consisting of 16,608 patients. Among them, 290 had breast cancer. After monitoring this group for 5.2 years, the relative risk of developing this type of neoplasm was found to be greater among those under estroprogestative therapy than those who only made use of estrogen therapy[79].

Another important study carried out from 1996 to 2001 was the Breast Cancer and hormone-replacement therapy in the Million women Study, which monitored 1,084,110 women. Out of this group, 9,364 were diagnosed with breast cancer, and 637 died from the disease after a follow-up of 2.6 and 4.1 years. The relative risk of developing this disease was 1.66 higher among users of hormone therapy. Also, the risk was even greater for women who made use of estrogen-progestogen combinations. The results also varied slightly depending on the doses of estrogen-progestogen or on use pattern, that is, continuous or sequential[80].

Regarding the risk of higher incidence of breast cancer among pill users, two studies, conducted in 1991 and 1996, analyzed epidemiological data from 50 thousand users and 100 thousand women from a control group and reported a slight increase in relative risk of 1.2 to 1.5 in the group of users. However, there was no increased risk for women who used the pill for more than ten years[81,82].

A recent study by Manson et al. examined the relationship between menopausal hormone therapy and placebo for a follow-up period of 5 to 7 years, and mortality risk up to 18 years (WH, randomized trials), monitored in 40 centers. The study counted with 27,347 women with mean age of 63.4 years, of whom 80.6% were white-skinned. There were 7,489 deaths. In one group, 8,506 women received conjugated estrogens (0.625 mg) and medroxyprogesterone acetate (10 mg) for 5.6 years *versus* 8,102 receiving placebo; in another trial, 5,310 women received only conjugated estrogens while 5,429 received placebo in a follow-up of 7.2 years. All-cause mortality was 27.1% in the hormone therapy group and 27.6% in the placebo group, while total mortality by cancer was 8.2% in the hormone therapy group and 8.5% in the placebo group. The study concluded that, among post-menopausal women, hormone therapy associated with conjugated estrogens and medroxyprogesterone, followed up for 5.6 years, or the use of

only conjugated estrogens for 7.2 years does not indicate higher risk of all-cause mortality, cardiovascular diseases, or even cancer mortality in up to 18 years of monitoring[83].

FINAL ANALYSIS

This wide range of existing chemicals — used as pesticides, and in the plastic, resin, dye, and pigment industries, among others — always deserve relevant observations, since they constitute examples of environmental contaminants and can be harmful to health.

These numerous substances seem to be responsible and act as co-authors and facilitators in the development of many diseases, breast carcinoma included.

In conclusion, it should be noted:

- The incidence of breast cancer, as well as other female genital neoplasms, has been increasing, and ED and environmental factors are suspected to have contributed to this scenario;
- There are critical periods in the development of breasts, when their susceptibility to endocrine actions is greater;
- For several rodents, there are crucial periods affecting breast development, rendering them prone to mammary neoplasms;
- Dioxins are chemical disruptors that delay pubertal development of breasts, according to evaluations in girls and rodents;
- Epidemiological studies indicate the importance of observing the effects of disruptors in women with higher sensitivity to breast cancer;
- There is a need for further studies that could test various combinations of ED based on their chemical structure and the evaluation of several lines of pre-cancerous tissue, in order to determine possible mechanisms of action related to the origin of breast cancer.

In 2015, the International Federation of Gynecology and Obstetrics (FIGO)[84] proposed various and important recommendations:

- Exposure to toxic chemicals has worldwide reach and is harmful to human reproduction and associated with various diseases;
- Preventing exposure to these substances should be a priority for all;
- Such toxic chemicals cross all country borders through food, water, wind, and different businesses and, thus, they act globally;
- Serious measures should be taken to avoid that the manufacturing of these substances leads to their constant release into the environment, rendering them dangerous to the health of a vulnerable population.

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