European Review for Medical and Pharmacological Sciences 2021; 25: 2898-2915

Pesticide exposure and gender discrepancy in breast cancer

C. LEDDA[1], M. BRACCI[2], P. LOVREGLIO[3], P. SENIA[1], M. LARROSA[4,5], B. MARTÍNEZ-JARRETA[5], V. RAPISARDA[1]

[1]Occupational Medicine, Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy
[2]Occupational Medicine, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy
[3]Occupational Medicine, Interdisciplinary Department of Medicine, University of Bari "Aldo Moro", Bari, Italy
[4]Internal Medicine Department, University Clinical Hospital Lozano Blesa, Zaragoza, Spain
[5]Forensic and Occupational Medicine, Faculty of Medicine, University of Zaragoza and Consolidated Research Group GIIS-063-Aragón, Zaragoza, Spain

Abstract. – OBJECTIVE: It is biologically plausible that occupational and environmental pesticide exposure may contribute to breast cancer risk. Persistent chemical compounds, such as pesticides, tend to be lipophilic and are detected in human breast milk and adipose tissue. Therefore, the present systematic review aims to clarify the gender difference in breast cancer concerning pesticide exposure.

MATERIALS AND METHODS: A total of 70 studies satisfied the inclusion criteria and were included in the systematic review.

RESULTS: From the studies analyzed, it was observed that exposure to pesticides could be a risk factor for breast cancer in women, in particular in young women and in women who experienced menarche at a young age. In contrast, no association was found for breast cancer in men. Female breast cancer is correlated with estrogen receptor-negative tumor characteristics. Breast cancer in men was no correlated with pesticide exposure.

CONCLUSIONS: Breast cancer in women has been linked to estrogen receptor positivity, but this positivity appears to be inversely related to fertility. The estrogen-like effects of organochlorine pesticides could be the cause of the observed gender differences.

Key Words:
Breast neoplasm, Mammary cancer, Breast tumor, Endocrine disruptors, Environmental exposure, Occupational exposure.

Introduction

Breast cancer (BC) is a group of diseases in which cells of the breast tissue change and divide in an uncontrolled manner, characteristically resulting in a lump or mass[1], consisting of four primary molecular subtypes and at least 21 different histological subtypes that differ in risk factors, staging, response to treatment, and outcomes[1].

Worldwide, there were approximately 2.1 million newly diagnosed female breast cancer (FBC) cases during 2018[2]. In the same year, more than 600,000 women died from FBC[2].

Hereditary and genetic factors are the most frequent risk factors in FBC, including an individual or familial history of FBC and/or ovarian cancer and inherited mutations (i.e., BRCA1, BRCA2, and further breast cancer susceptibility genes). Other known risk factors for FBC are connected with menstruation (early age at menarche, age at menopause), reproduction (nulliparity, late age at first at childbirth, and fewer children), exogenous hormone intake (oral contraceptive use and hormone surrogate therapy), diet (alcohol intake), anthropometry (higher weight, weight gain during adulthood, and body fat distribution), shift work, and various occupational and environmental risk factors[3-12]; while breastfeeding and physical activity are recognized as protective factors[3].

BC is a pathology that can also affect men[13]. Male breast cancer (MBC) is infrequent, representing 1% of cancers that happen in men and approximately 1% of all BC worldwide[14-18]. Fewer than 0.2% of cancer-related deaths in men can be attributed to MBC[19,20].

However, the incidence and prevalence of MBC fluctuate by race and ethnicity[13]. Indefi-

Corresponding Author: Caterina Ledda, Ph.D; e-mail: caterina.ledda@unict.it

nite male populations, such as African Americans, have elevated rates of MBC in contrast with equivalent Caucasian, Hispanic, or Asian/Pacific Islander populations[13]. The median age at BC diagnosis is characteristically higher in men than in women, at 68 and 62, respectively[13].

The first identification of MBC frequently occurs at a later stage than in FBC. MBC is often further advanced at the instance of identification and may include, for example, a superior cancer dimension, lymph node involvement, and remote metastases[14,15,21-26].

Genetic risk factors for MBC are similar, but not identical, to those in women. Family history is pertinent for both[21,22], and BRCA2 mutations and rearrangements play an important role in MBC[23-26]. Between 5-10% of men with BRCA2 mutations can develop BC[27-31]. However, one investigation[32] of 102 Italian MBC patients established no BRCA1 or BRCA2 reorganizations. Circumstances that modify the ratio of estrogen to androgen have been connected to MBC. Klinefelter's syndrome[33,34], exogenous estrogen or testosterone use[35], obesity[34,36-38], orchitis/epididymitis[34], finasteride[39,40], and prostate cancer treated with estrogens, have been linked with MBC[41]. Participating in sports appears to decrease risk[34]. Some investigations have not established an association between smoking, alcohol intake, and MBC[34,38]. Epidemiological studies have evaluated occupational exposure, as well as exposure to electromagnetic fields[42-43], heat[44], and polycyclic aromatic hydrocarbons, pesticides, and other chemicals[45-47] as possible risk factors for MBC. However, the data have been varied and questionable[48,49].

It is biologically plausible that occupational and environmental exposure may contribute to BC risk; in particular, persistent chemical compounds (i.e., pesticides) tend to be lipophilic and are detected in human breast milk and adipose tissue[50-52]. As an endocrine disruptor, pesticide exposure may cause BC by altering hormonal activity or causing epigenetic damage[53]. Therefore, the present systematic review aims to clarify the gender differences in BC with regard to pesticide exposure.

Materials and Methods

This systematic review was carried out in accordance with the PRISMA statement[54].

Literature Search

SCOPUS, Medline (using PubMed as the search engine), Embase, and Web of Science databases were examined to identify relevant research available until November 1, 2020, to investigate the association between pesticide exposure and BC, with BC as the principal outcome.

A MeSH term was used with the following entry terms: "Breast Neoplasms" AND "Pesticides"; "Breast Neoplasms" AND "Agrochemicals"; "Breast Neoplasms" AND "Pesticide Residues".

A search for research manuscripts that were appropriate for inclusion in this systematic review was conducted, and the papers of significance therein were collected and reviewed.

Inclusion and Exclusion Criteria

The subsequent inclusion criteria were assumed: (1) studies that assessed BC in relation to pesticide exposure assessments. The following exclusion criteria were applied: (1) animal studies, (2) scientific articles that are not published in the English language; and (3) reviews, conference abstracts or letters to the editor.

For matching studies, only articles with supplementary detailed information were included.

Quality Assessment and Data Extraction

Two reviewers (CL and VR) recovered articles independently. The title, abstract, and full text of each potentially relevant study was reviewed. Any divergence on the eligibility of the papers was determined through debate or by consulting an additional reviewer (MB). The following information was extracted from all papers: authors, year of publication, exposure, study design, period, population observed, age population observed, country, and conclusion of the study.

Results

Characteristics of Eligible Studies

After a search of the scientific literature by the reviewers, 312 research papers were collected, and five were replicated. A total of 307 were investigated following a review of the title and abstract, and 237 studies were deemed ineligible after reviewing the manuscript. In summary, 70 studies satisfied the inclusion criteria and were included in the systematic review[55-121]. A flowchart showing the choice of studies is presented in Figure 1.

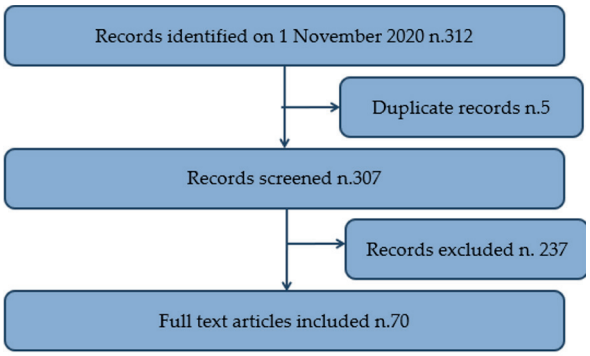

Figure 1. Flow diagram illustrating included and excluded studies in this systematic review.

Researchers from various countries conducted the investigations: 35 in the USA; four each in Canada, Spain, and the UK; three each in Australia, Brazil, Canada, China, and Denmark; two each in Belgium, Germany, Japan, Italy, and Mexico; and one each in Colombia, Egypt, France, Greece, India, the Netherlands, Norway, Palestine, Sweden, Switzerland, and Taiwan Figure 2).

The study designs were as follows: 43 case-control, 12 cohorts, eight mortality cohort, six incidence cohort, two ecological, and one observational study.

To highlight gender differences, it was decided to divide the studies between FBC (Table I) and MBC (Table II).

Female Breast Cancer

The studies included 63 articles that aimed to establish an association between FBC and pesticide exposure. The studies were performed over a long period: 1960-2019. In recent years, the pesticides used have varied considerably; some have not been available for a long time, while others have been introduced to the market more recently. Furthermore, pesticides are persistent pollutants in the environment, and current exposure may be affected by remote exposure because of residual contamination in some areas of the globe[50].

A total of 13 (21%) studies investigated work-related exposure in women[55,58,64,65,67,69,75-78,88,107,112], 46 (73%) investigated environmental exposure[56,57,59-63,66,68,71-74,79,81,83-87,89-104,106,108-111,113-118], and four (6%) investigated both exposure factors[70,80,82,105].

A total of 25 studies analyzed pesticide metabolites in serum and BC incidence[56,57,60-63,66,68,72-74,81,92,96,98,104,108,110,111,116-118], and five measured the concentrations of pesticides (metabolites) in BC tissue[70,87,89,91,113].

By analyzing the results of the studies, some opposing results emerged. In particular, 39 (62%) investigations underline an association between exposure to pesticides and FBC[55,56,59,69-71,74-83,86,87,89,91,93-95,97-99,101,103,106-118], whereas the other 24 (38%) highlight the opposite[56-59,60-68,72,73,84,85,88,90,92,96,100,102,104,105].

The association between FBC and pesticide exposure was asserted by 10 occupational and 29

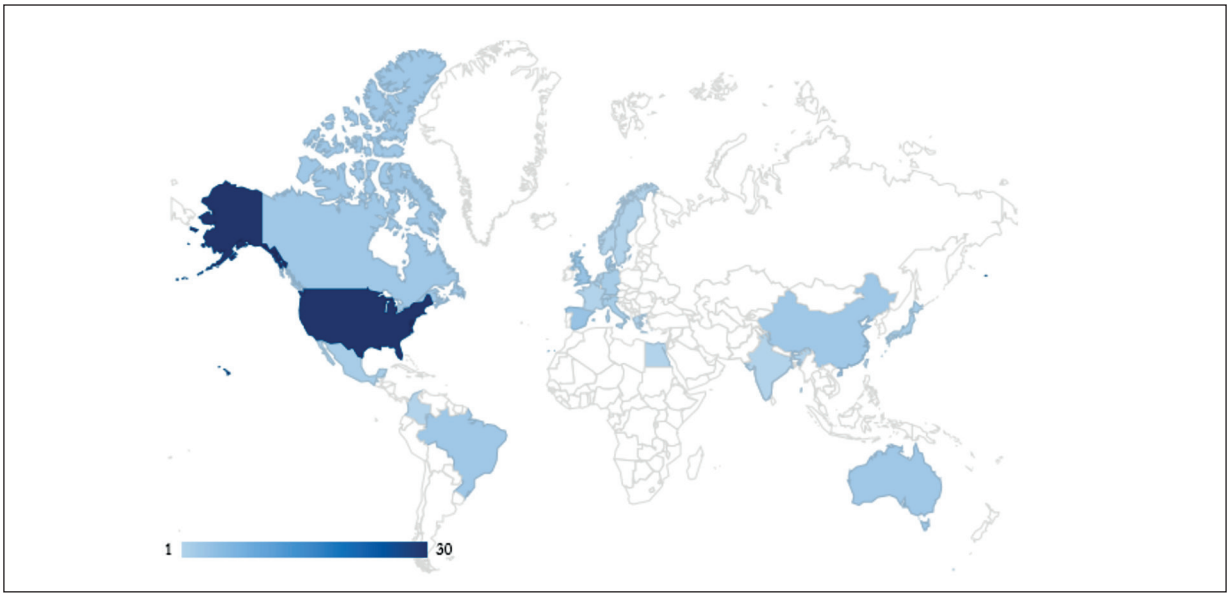

Figure 2. Graphical map of the geographical distribution of the selected studies.

Table I. Main characteristics of eligible studies of FBC.

Reference	Exposure	Study design	Period	Population observed	Age (years)	Country	Conclusions
Davis et al[55]	Occupational	Mortality cohort study	1968-1986	163	n.d.	USA, Japan, UK, France, Italy, and West Germany	Probable association
Wolff et al[56]	Environmental	Case-control study	1985-1991	58	n.d.	USA	BC was strongly associated with high DDE serum concentration
Krieger et al[57]	Environmental	Case-control study	1960-1990	150	n.d.	USA	BC was not associated with DDE serum concentration
Wiklund and Dich[58]	Occupational	Incidence cohort study	1971-1987	4747	n.d.	Sweden	No association with exposure to pesticides
Kettles et al[59]	Environmental	Incidence cohort study	1991-1994	n.d.	n.d.	USA	Relationship between exposure to triazine and FBC
Van 'T Veer et al[60]	Environmental	Case-control study	1991-1992	265	50-74	Germany, Netherlands, Northern Ireland, Switzerland, Spain	BC was not associated with DDE serum concentration in postmenopausal women
López-Carrillo et al[61]	Environmental	Case-control study	1994-1996	141	20-79	Mexico	BC was not associated with DDE serum concentration
Hunter et al[62]	Environmental	Case-control study	1989-1992	236	59 (43-69)	USA	BC was not associated with DDE serum concentration
Olaya-Contreras et al[63]	Environmental	Case-control study	1995-1996	153	26-75	Colombia	BC was associated with DDE serum concentration
Petralia et al[64]	Occupational	Incidence cohort study	1980-1984	69	n.d.	China	Exposure to pesticides was not related to the risk of FBC
Fleming et al[65]	Occupational	Mortality cohort study	1975-1993	4	n.d.	USA	No association with exposure to pesticides
Mendonça et al[66]	Environmental	Case-control study	1995-1996	177	57 (30-75)	Brazil	BC was not associated with DDE serum concentration
Fleming et al[67]	Occupational	Incidence cohort study	1975-1993	26	n.d.	USA	No association with exposure to pesticides
Ward et al[68]	Environmental	Case-control study	1975-1993	300	41.1±6.8	Norway	BC was not associated with DDE serum concentration
Band et al[69]	Occupational	Case-control study	1980-1995	2038	n.d.	Canada	Positive association with pesticide exposure
Aronson et al[70]	Environmental and occupational	Case-control study	1995-1997	430	57.7 ± 11.6 (cases) 53.9 ± 10.9 (controls)	Canada	Association with Mirex and DDE concentration in breast adipose tissue

Continued

Table I *(Continued)*. Main characteristics of eligible studies of FBC.

Reference	Exposure	Study design	Period	Population observed	Age (years)	Country	Conclusions
HØyer et al[71]	Environmental	Cohort study	1976-1992	717	54.6) (mean	Denmark	Possible association between organochlorine exposure and BC risk
Stellman et al[72]	Environmental	Case-control study	1994-1996	1030	n.d.	USA	BC was not associated with DDE serum concentration
Millikan et al[73]	Environmental	Case-control study	1993-1996	1730	50.8 (23-74)	USA	BC was not associated with DDE serum concentration
Demers et al[74]	Environmental	Case-control study	1994-1997	534	53 ± 10	Canada	p,p′-DDE may increase BC aggressiveness
Duell et al[75]	Occupational	Case-control study	1993-1996	1652	20-74	USA	Positive association with pesticide exposure
Dolapsakis et al[76]	Occupational	Cohort study	1988-1933	1053	40-75	Greece	Exposed have a higher risk of breast lesions
Janssens et al[77]	Occupational	Mortality cohort study	1985-1994	589	n.a.	Belgium	Positive association with pesticide exposure
Thomas et al[78]	Occupational	Mortality cohort study	1980-1990	2548	15-65	USA	Positive association with pesticide exposure
Mathur et al[79]	Environmental	Case-control study	2002	185	21-70	India	Positive association with pesticide exposure
Safi[80]	Environmental and occupational	Observational study	1990-1999	796	0-65+	Palestine	Association with exposure to pesticides
Charlier et al[81]	Environmental	Case-control study	1999-2000	409	54 ± 12	Belgium	BC was associated with serum pesticide metabolite concentration
Brody et al[82]	Environmental and occupational	Case-control study	1988-1995	2081	60-80	USA	Increased risk only for pesticide applicators
O'Leary et al83	Environmental	Case-control study	1980-1992	315	61.1 ± 11.4	USA	Association with BC only in long-term resident within 1 mile of hazard waste sites containing organochlorine pesticides
Muir et al[84]	Environmental	Ecological study	1989-1991	n.d.	> 45	UK	No association between pesticide exposure and BC
Reynolds et al[85]	Environmental	Cohort study	1995	133.479	40-59	USA	No association between pesticide exposure and BC
Mills et al[86]	Environmental	Case-control study	1988-2001	768	n.d.	USA	Chlordane, malathion, and 2,4-D were associated with increased risk for BC (stronger in young women)
Raaschou-Nielsen et al[87]	Environmental	Case-control study	1993-1997	818	57.4 ± 4.0	Denmark	Correlation between estrogen receptor-negative BC and high organochlorine concentrations in breast tissue
Engel et al[88]	Occupational	Cohort study	1993-1997	30454	18-96	USA	No association between pesticide exposure and BC
Zumbado et al[89]	Environmental	Cohort study	1997-1998	783	6-75	Spain	Possible association between estrogenic BC and p,p′-DDT concentration

Continued

Table I *(Continued)*. Main characteristics of eligible studies of FBC.

Reference	Exposure	Study design	Period	Population observed	Age (years)	Country	Conclusions
Alavanja et al[90]	Environmental	Cohort study	1993-2002	52395	n.d.	USA	No association between pesticide exposure and BC
Waliszewski et al[91]	Environmental	Case-control study	2004	254	49	Mexico	Correlation between BC and organochlorine concentrations in breast tissue.
Rubin et al[92]	Environmental	Case-control study	1981-1987	126	< 54	USA	BC was not associated with DDE serum concentration
Khanjani et al[93]	Environmental	Ecological study	1983-2002	797	n.d.	Australia	Limited association between BC and organochlorine pesticide exposure
Teitelbau et al[94]	Environmental	Case-control study	1993-1997	1508	n.d.	USA	Association between pesticide exposure and BC
Cohn et al[95]	Environmental	A prospective nested case-control study	1959-1967	258	n.d.	USA	Exposure to p,p′-DDT early in life may increase BC risk.
Itoh et al[96]	Environmental	Case-control study	2001-2005	806	53.8 ± 0.5	Japan	No association with serum pesticide metabolite concentration
Jacome et al[97]	Environmental	Cohort study	2005-2008	110	20-35	Brazil	Association between pesticide exposure and BC
Xu et al[98]	Environmental	Cohort study	1999-2004	4172	20-75	USA	BC was associated with serum organochlorine pesticide metabolite concentration
Zota et al[99]	Environmental	Case-control study	1988-1995	1508	40-85	USA	Moderate association between pesticide exposure and BC
Farooq et al[100]	Environmental	Case-control study	1994-1996	1205	50-70	USA	No association between pesticide exposure and BC
Waggoner et al[101]	Environmental	Mortality cohort study	1993-2007	89656	n.a.	USA	Association between pesticide exposure and BC
Ashley-Martin et al[102]	Environmental	Case-control study	1999-2002	828	54.8 ± 53.4-56.0	Canada	No association between pesticide exposure and BC
El-Zaemey et al[103]	Environmental	Case-control study	2009-2011	2912	30-75	Australia	Association between pesticide exposure and BC at a young age of exposure
Holmes et al[104]	Environmental	Case-control study	1999-2002	170	30-88	USA	No association with serum pesticide metabolite concentration
El-Zaemey et al[105]	Environmental and occupational	Case-control study	2009-2011	2912	30-75	Australia	No association between pesticide exposure and BC
Parrón et al[106]	Environmental	Case-control study	1998-2005	34191	n.d.	Spain	Association between pesticide exposure and BC
Lerro et al[107]	Occupational	Cohort study	1993-1997	30003	n.d.	USA	Association between pesticide exposure and BC
Cohn et al[108]	Environmental	A prospective nested case-control study	1959-1967	472	n.d.	USA	Association between in utero DDT exposure and risk of BC in young women and possible association with more aggressive BC
Salerno et al[109]	Environmental	Case-control study	2002-2009	12378	25-79	Italy	Association between pesticide exposure and BC

Continued

Table I ***(Continued).*** Main characteristics of eligible studies of FBC.

Reference	Exposure	Study design	Period	Population observed	Age (years)	Country	Conclusions
He et al[110]	Environmental	Case-control study	2015-2016	102	52.4 ± 10.6	China	BC was associated with serum pesticide metabolite concentration
Wielsøe et al[111]	Environmental	Case-control study	2000-2003 2011-2014	161	52±9	Denmark	BC was associated with blood pesticide metabolite concentration
Engel et al[112]	Occupational	Cohort study	1993-1997	52394	n.d.	USA	Several organophosphate insecticides were associated with elevated BC risk
Eldakroory et al[113]	Environmental	Cohort study	2014-2015	70	n.d.	Egypt	BC was associated with organochlorine pesticides in tissue specimens
Chang et al[114]	Environmental	Cohort study	1996-2013	3141	n.d.	Taiwan	BC was associated with DDT exposure in childhood
Silva et al[115]	Environmental	Case-control study	2017-2018	351	54.3 8.4 (cases) 51.1 ± 10.6 (controls)	Brazil	Women exposed to pesticides aged over 50 years and who experienced early menarche had higher BC risk
Huang et al[116]	Environmental	Case-control study	2014-2016	374	52.00 ± 9.89 (cases) 48.64 ± 10.88 (controls)	China	Association with p,p'-DDT, and p,p'-DDE and BC risk
Cohn et al117	Environmental	A prospective nested case-control study	1959-1967	585	n.d.	USA	p,p'-DDT is a risk factor for BC through age 54 years
Cohn et al[118]	Environmental	A prospective nested case-control study	(1959-1967) 1998	266	<50 years	USA	Association with p,p'-DDT, and p,p'-DDE and BC risk

Table II. Main characteristics of eligible studies of MBC.

Reference	Exposure	Study design	Period	Population observed	Age (years)	Country	Conclusions
Cocco et al[119]	Occupational	Case-control study	1985-1986	3	n.d.	USA	No association with exposure to pesticides
Fleming et al[120]	Occupational	Mortality cohort study	1975-1993	0	/	USA	No cases of MBC were observed
Fleming et al[121]	Occupational	Incidence of cohort study	1975-1993	2	n.d.	USA	No association with exposure to pesticides
Safi[80]	Environmental and occupational	Observational study	1990-1999	5	2 (15-44 y) 2 (55-64 y) 1 (+65 y)	Palestine	No association with exposure to pesticides
Fleming et al[122]	Occupational	Mortality cohort study	1986-1994	0	/	USA	No cases of MBC were observed
Macfarlane et al[123]	Occupational	Incidence cohort study	1991-2002	6	n.d.	UK Gulf war veterans	No association with exposure to pesticides
Villeneuve et al[124]	Occupational	Cohort study	1995-1997	27	n.d.	Europe	No association with exposure to pesticides
Waggoner et al[101]	Environmental and occupational	Mortality study	1993-1997	12	n.d.	USA	Negative association
Parrón et al[125]	Environmental	Case-control study	1998-2005	n.d.	n.d.	Spain	No significant association
Salerno et al[109]	Environmental and occupational	Case-control study	2002-2009	1	n.d.	Italy	Non-analyzable data

environmental studies. Beyond investigating the correlation between FBC and pesticide exposure, six focused on occupational exposure and 18 on environmental exposure.

By analyzing the subgroup of 30 reports that involved measuring pesticide metabolites in biological samples, it was observed that 19 (63%) indicated an association between pesticide metabolites and FBC, and 11 (37%) showed no association. In particular, the investigations affirming a strong association were the most recent, and therefore were performed using more reliable analytical methods such as gas chromatography-mass spectrometry and liquid chromatography-mass spectrometry. Furthermore, studies that show a positive correlation between pesticide exposure and FBC highlight a strong association with the onset of carcinoma at a young age and with organochlorine pesticides.

Among the studies in which a statistically significant correlation was found between BC and pesticides, the latter were usually organochlorine pesticides.

Finally, it is possible to affirm that there can be a link between exposure to some classes of pesticides and the onset of FBC.

Male Breast Cancer

For this systematic review, 10 investigations were studied. Table II lists the main characteristics of eligible studies for MBC.

Cocco et al[119] investigated the link between MBC risk and some occupational risk factors, including pesticides; they noticed a negative association between occupational exposure to herbicides and other pesticides.

Fleming et al[120-122] conducted three studies on health outcomes in pesticide applicators, two on mortality[120,122], and one on incidence[121]. No cases of MBC were reported in a mortality study[120-122]. A total of two cases were observed in the incidence study[121], but no correlation was found between pesticide exposure and MBC.

Safi[80] described the association between chronic exposure to pesticides and recorded cases of cancer in an area where pesticides were used extensively. An incidence of 0.1% was reported, but also, in this case, no association between exposure to pesticides and MBC was established.

An incidence cohort study among UK Gulf war veterans was carried out by Macfarlane et al[123], who observed six cases of MBC, but no association was reported with pesticide exposure.

Later, a specific study on MBC and occupational exposure to endocrine-disrupting chemicals, including pesticides, in eight European Countries was conducted by Villenueve et al[124]. Exposure to pesticides was not associated with MBC.

Of the three mortality cohort studies in licensed pesticide users in the USA, in the two conducted by Fleming et al[120-122], no cases of MBC were found, while in the study led by Wagoner et al[101], 11 cases were found, but no association with previous exposure to pesticides was detected.

Environmental exposure to pesticides and cancer risk was evaluated by Parron et al[125] but no significant association was found for MBC.

Finally, a population-based case-control study investigated the association between farming (a proxy for pesticide exposure) and cancer in Italy[109], but they found only one case of MBC.

Therefore, in light of the results obtained, no study correlated pesticide exposure with MBC.

Discussion

Exposure to pesticides has become ubiquitous for workers and the general population because of their extensive use. The routes of pesticide exposure are different between occupational and environmental exposure, and it appears that the effects of exposure are also different for men and women.

Pesticides have been studied as a risk factor for many chronic-degenerative diseases[126-140].

From the studies analyzed, we can affirm that exposure to pesticides could be a risk factor for FBC, in particular in young women and in women who had menarche at a young age. In contrast, no association was found for MBC.

Organochlorine pesticides, including 1,1'-(2,2,2-Trichloroethane-1,1-diyl)bis(4-chlorobenzene) (DDT), were used extensively in the USA from the early 1940s until the 1960s for insect control (i.e., residential use) and outdoor (i.e., agriculture). The use of DDT peaked in the USA in the early 1960s and was prohibited in 1972. Other organochlorines include pesticides used in lesser amounts, such as lindane and hexachlorobenzene.

Organochlorine pesticides degrade slowly but are lipid-soluble; therefore, they bioaccumulate in the food chain and may be observed in human adipose tissue, blood, and breast milk. The most

prevalent organochlorine residue usually found in human tissues is 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE), the major metabolite of DDT[132].

DDE was found in the serum and breast adipose tissue of patients with FBC in various studies and often correlated with FBC[56,57,60-63,66,68,72-75,81,92,96,98,104,108,110,111,116-118]. However, in a lower number of studies, this association was not observed[70,87,89,91,113].

The studies that do not support correlation are older papers and were therefore conducted with less precise analytical methods.

Recently, many research groups' interest has been focused on the potential of various chemicals to act as "endocrine disruptors." An endocrine disruptor is a compound that interferes with the endocrine system's role by mimicking a hormone, interrupting the effects of a hormone, or by stimulating or inhibiting the release or transport of hormones[143]. Several organochlorine pesticide metabolites, including DDE, are screened as endocrine disruptors because they showed slightly estrogenic or antiestrogenic activity in experimental investigations[144-145]. Furthermore, carcinogenic behaviors have been highlighted in animal models[146-147].

In 1993, a case-control study carried out by Wolff et al[56] in New York found the highest serum levels of DDE in FBC compared with a paired woman without BC. Since 1993, other research groups have attempted to confirm the associations observed in the Wolff et al study[56], but these did not find the same association[57,60-62,66,68,72,73,92,96].

In a pooled analysis of other investigations[63,70,74,86,87], the relative risks for FBC were significantly associated with women in the highest quintiles for DDE concentration.

Recent researches[89,91,98,108-118] have highlighted the possibility that exposure to organochlorine pesticides may underly higher rates of FBC.

Exposure to organochlorine pesticides appears to amplify the risk of FBC. A study carried out by Raaschou-Nielsen et al[87] on FBC grouped by tumor characteristics such as estrogen receptor and progesterone receptor status, correlated high DDE concentrations with estrogen receptor-negative FBC.

The etiology of estrogen receptor-negative FBC is unknown but is associated with a young age of onset and early menarche[148,149].

Generally, MBC was highly estrogen receptor positive compared with FBC. FBC has also been linked to estrogen receptor positivity, but this positivity appears to be inversely related to female fertility. Typically, it is known that older women are more likely to be estrogen receptor-positive[150].

The associations observed by Raaschou-Nielsen et al[87] seem contrary to the extensively established mechanism through which estrogens may cause BC by binding with estrogen receptors[151]. The mechanism, therefore, remains unclear. Some organochlorine pesticides and several of their metabolites have been found to stimulate estrogen-like effects in exposed humans. Consequently, they could be involved in endocrine pathologies connected with estrogenic effects, such as BC[152-154].

Cohn et al[95] and other research groups[155-158] have provided more experimental evidence on the timing of environmental exposure to pesticides during susceptible periods, also called "windows," including in utero, and in childhood, puberty, and pregnancy, which can cause a change in the regulation of breast development that can provoke BC in adulthood. It is impossible to estimate the role of genetic susceptibility; however, from this review's results, pesticide exposure and BC could be associated with in utero exposure and early BC. It is probable that pesticides may either provoke a non-germline genetic susceptibility or otherwise interact with an unknown genetic susceptibility. The recognized association between BC and protracted exposure to estrogens suggests that environmental estrogens, such as organochlorine pesticides, could play a critical role in the cellular and molecular changes that happen throughout breast carcinogenesis. These alterations change healthy cells to latent tumor cells by shifting the genetic material that facilitates their proliferation[159-164]. Furthermore, there is evidence[151] to support estrogen receptor-independent mechanisms in estrogen-mediated BC development through the production of genotoxic estrogen metabolites, which can provoke DNA damage and/or form DNA adducts[151].

This finding provides the biological foundation to support the findings of the studies that link exposure to chlorinated pesticides to BC in the present systematic review.

The current review provides a foundation for the link between exposure to chlorinated pesticides and FBC.

The present study's limitations include a loss of information about the exposure that occurred many years before the onset of BC; epidemiolog-

ical studies are conducted in different countries, which use different products and cultivation systems. Furthermore, certain studies do not report details on pesticide exposure or their concentration in biological fluids and/or tissues.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

The authors declare that there is no funding available for the publication of this paper.

References

1) https://www.who.int/cancer/detection/breastcancer/en/ (Accessed on 30/01/2020)
2) Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394-424.
3) Brinton LA, Gaudet MM, Gierach GL. Breast cancer. In: Schottenfeld and Fraumeni Cancer epidemiology and prevention, fourth edition, Oxford Scholarship, 2017; pp. 861-888.
4) Bracci M, Ciarapica V, Zabaleta ME, Tartaglione MF, Pirozzi S, Giuliani L, Piva F, Valentino M, Ledda C, Rapisarda V, Stevens RG, Santarelli L. BRCA1 and BRCA2 gene expression: diurnal variability and influence of shift work. Cancers 2019; 11: 1146.
5) Bray F, McCarron P, Parkin DM. The changing global patterns of female breast cancer incidence and mortality. Breast Cancer Res 2004; 6: 229-239.
6) Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative Randomized Controlled Trial. JAMA 2002; 288: 321-333.
7) Leonardi GC, Rapisarda V, Marconi A, Scalisi A, Catalano F, Proietti L, Travali S, Libra M, Fenga C. Correlation of the risk of breast cancer and disruption of the circadian rhythm (review). Oncol Rep 2012; 28: 418-428.
8) Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K. Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol 2017; 3: 1228-1236.
9) Hjerkind KV, Ellingjord-Dale M, Johansson ALV, Aase HS, Hoff SR, Hofvind S, Fagerheim S, Dos-Santos-Silva I, Ursin G. Volumetric mammographic density, age-related decline, and breast cancer risk factors in a national breast cancer screening program. Cancer Epidemiol Biomarkers Prev 2018; 27: 1065-1074.
10) Holm J, Eriksson L, Ploner A, Eriksson M, Rantalainen M, Li J, Hall P, Czene K. Assessment of breast cancer risk factors reveals subtype heterogeneity. Cancer Res 2017; 77: 3708-3717.
11) Zhang L, Huang Y, Feng Z, Wang X, Li H, Song F, Liu L, Li J, Zheng H, Wang P, Song F, Chen K. Comparison of breast cancer risk factors among molecular subtypes: a case-only study. Cancer Med 2019; 8: 1882-1892.
12) Chopra-Tandon N, Wu H, Arcaro KF, Sturgeon SR. Relationships between global DNA methylation in circulating white blood cells and breast cancer risk factors. J Cancer Epidemiol 2017; 2017: 2705860.
13) Gucalp A, Traina TA, Eisner JR, Parker JS, Selitsky SR, Park BH, Elias AD, Baskin-Bey ES, Cardoso F. Male breast cancer: a disease distinct from female breast cancer. Breast Cancer Res Treat 2019; 173: 37-48.
14) Korde LA, Zujewski JA, Kamin L, Giordano S, Domchek S, Anderson WF, Bartlett JMS, Gelmon K, Nahleh Z, Bergh J, Cutuli B, Pruneri G, McCaskill-Stevens W, Gralow J, Hortobagyi G, Cardoso F. Multidisciplinary meeting on male breast cancer: summary and research recommendations. J Clin Oncol 2010; 28: 2114-2122.
15) Cutuli B. Strategies in treating male breast cancer. Expert Opin Pharmacother 2007; 8: 193-202.
16) Gennari R, Curigliano G, Jereczek-Fossa BA, Zurrida S, Renne G, Intra M, Galimberti V, Luini A, Orecchia R, Viale G, Goldhrisch A, Veronesi U. Male breast cancer: a special therapeutic problem. Anything new? (review). Int J Oncol 2004; 24: 663-670.
17) Fentiman IS, Fourquet A, Hortobagyi GN. Male breast cancer. Lancet 2006; 367 595-604.
18) Yoney A, Kucuk A, Unsal M. Male breast cancer: a retrospective analysis. Cancer Radiother 2009; 13: 103-107.
19) Weiss JR, Moysich KB, Swede H. Epidemiology of male breast cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 20-26.
20) Burga AM, Fadare O, Lininger RA, Tavassoli FA. Invasive carcinomas of the male breast: a morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases. Virchows Arch 2006; 449: 507-512.
21) Darkeh MHSE, Azevedo E. Male breast cancer clinical features, risk factors, and current diagnostic and therapeutic approaches. Int J Clin Med 2014; 5: 1068-1086.
22) Giotta F, Acito L, Candeloro G, Del Medico P, Gadaleta-Caldarola G, Giordano G, Gueli R, Lugini A, Magri V, Mandarà M, Masci G, Pisconti S,

Pistelli M, Rizzi A, Salesi N, Schirone A, Scognamiglio G, Tedeschi M, Zucchinelli P. Eribulin in male patients with breast cancer: the first report of clinical outcomes. Oncologist 2016; 21: 1298-1305.

23) Donegan WL, Redlich PN, Lang PJ, Gall MT. Carcinoma of the breast in males: a multiinstitutional survey. Cancer 1998; 83: 498-509.

24) Joshi MG, Lee AKC, Loda M, Camus MG, Pedersen C, Heatley GJ, Hughes KS. Male breast carcinoma: an evaluation of prognostic factors contributing to a poorer outcome. Cancer 1996; 77: 490-498.

25) Arslan UY, Öksüzoğlu B, Özdemir N, Aksoy S, Alkiş N, Gök A, Kaplan MA, Gümüş M, Berk V, Uncu D, Baykara M, Çolak D, Üyetürk U, Türker I, Işikdoğan A. Outcome of non-metastatic male breast cancer: 118 patients. Med Oncol 2012; 29: 554-560.

26) Anderson WF, Jatoi I, Tse J, Rosenberg PS. Male breast cancer: a population-based comparison with female breast cancer. J Clin Oncol 2010; 28: 232-239.

27) Rudlowski C. Male breast cancer. Breast Care 2008; 3: 183-189.

28) Rizzolo P, Silvestri V, Tommasi S, Pinto R, Danza K, Falchetti M, Gulino M, Frati P, Ottini L. Male breast cancer: genetics, epigenetics, and ethical aspects. Ann Oncol 2013; 24 Suppl 8: viii75-viii82.

29) Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P, Bishop DT, Weber B, Lenoir G, Chang-Claude J, Sobol H, Teare MD, Struewing J, Arason A, Scherneck S, Peto J, Rebbeck TR, Tonin P, Neuhausen S, Barkardottir R, Eyfjord J, Lynch H, Ponder BAJ, Gayther SA, Birch JM, Lindblom A, Stoppa-Lyonnet D, Bignon Y, Borg A, Hamann U, Haites N, Scott RJ, Maugard CM, Vasen H, Seitz S, Cannon-Albright LA, Schofield A, Zelada-Hedman M. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet 1998; 62: 676-689.

30) Greene MH. Genetics of breast cancer. Mayo Clin Proc 1997; 72: 54-65.

31) Silvestri V, Barrowdale D, Mulligan AM, Neuhausen SL, Fox S, Karlan BY, Mitchell G, James P, Thull DL, Zorn KK, Carter NJ, Nathanson KL, Domchek SM, Rebbeck TR, Ramus SJ, Nussbaum RL, Olopade OI, Rantala J, Yoon S-, Caligo MA, Spugnesi L, Bojesen A, Pedersen IS, Thomassen M, Jensen UB, Toland AE, Senter L, Andrulis IL, Glendon G, Hulick PJ, Imyanitov EN, Greene MH, Mai PL, Singer CF, Rappaport-Fuerhauser C, Kramer G, Vijai J, Offit K, Robson M, Lincoln A, Jacobs L, Machackova E, Foretova L, Navratilova M, Vasickova P, Couch FJ, Hallberg E, Ruddy KJ, Sharma P, Kim S-, Teixeira MR, Pinto P, Montagna M, Matricardi L, Arason A, Johannsson OT, Barkardottir RB, Jakubowska A, Lubinski J, Izquierdo A, Pujana MA, Balmaña J, Diez O, Ivady G, Papp J, Olah E, Kwong A, Nevanlinna H, Aittomäki K, Perez Segura P, Caldes T, Van Maerken T, Poppe B, Claes KBM, Isaacs C, Elan C, Lasset C, Stoppa-Lyonnet D, Barjhoux L, Belotti M, Meindl A, Gehrig A, Sutter C, Engel C, Niederacher D, Steinemann D, Hahnen E, Kast K, Arnold N, Varon-Mateeva R, Wand D, Godwin AK, Evans DG, Frost D, Perkins J, Adlard J, Izatt L, Platte R, Eeles R, Ellis S, Hamann U, Garber J, Fostira F, Fountzilas G, Pasini B, Giannini G, Rizzolo P, Russo A, Cortesi L, Papi L, Varesco L, Palli D, Zanna I, Savarese A, Radice P, Manoukian S, Peissel B, Barile M, Bonanni B, Viel A, Pensotti V, Tommasi S, Peterlongo P, Weitzel JN, Osorio A, Benitez J, McGuffog L, Healey S, Gerdes A, Ejlertsen B, Hansen TVO, Steele L, Ding YC, Tung N, Janavicius R, Goldgar DE, Buys SS, Daly MB, Bane A, Terry MB, John EM, Southey M, Easton DF, Chenevix-Trench G, Antoniou AC, Ottini L. Male breast cancer in BRCA1 and BRCA2 mutation carriers: pathology data from the consortium of investigators of modifiers of BRCA1/2. Breast Cancer Res 2016; 18: 15.

32) Falchetti M, Lupi R, Rizzolo P, Ceccarelli K, Zanna I, Calò V, Tommasi S, Masala G, Paradiso A, Gulino A, Giannini G, Russo A, Palli D, Ottini L. BRCA1/BRCA2 rearrangements and CHEK2 common mutations are infrequent in italian male breast cancer cases. Breast Cancer Res Treat 2008; 110: 161-167.

33) Karami F, Mehdipour P. A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Bio Med Res Int 2013; 2013: 928562.

34) Pritzlaff M, Summerour P, McFarland R, Li S, Reineke P, Dolinsky JS, Goldgar DE, Shimelis H, Couch FJ, Chao EC, LaDuca H. Male breast cancer in a multi-gene panel testing cohort: insights and unexpected results. Breast Cancer Res Treat 2017; 161: 575-586.

35) Liang M, Zhang Y, Sun C, Rizeq FK, Min M, Shi T, Sun Y. Association between CHEK2*1100delC and breast cancer: a systematic review and meta-analysis. Mol Diagn Ther 2018; 22: 397-407.

36) Severson TM, Zwart W. A review of estrogen receptor/androgen receptor genomics in male breast cancer. Endocr Relat Cancer 2017; 24: R27-R34.

37) Wu Q, Li J, Zhu S, Wu J, Li X, Liu Q, Wei W, Sun S. Poorer breast cancer survival outcomes in males than females might be attributable to tumor subtype. Oncotarget 2016; 7: 87532-87542.

38) El-Tamer MB, Komenaka IK, Troxel A, Li H, Joseph K, Ditkoff B, Schnabel FR, Kinne DW. Men with breast cancer have better disease-specific survival than women. Arch Surg 2004; 139: 1079-1082.

39) Marchal F, Salou M, Marchal C, Lesur A, Desandes E. Men with breast cancer have same disease-specific and event-free survival as women. Ann Surg Oncol 2009; 16: 972-978.

40) Bagley CS, Wesley MN, Young RC, Lippman ME. Adjuvant chemotherapy in males with cancer of

the breast. Am J Clin Oncol Cancer Clin Trials 1987; 10: 55-60.

41) Scott-Conner CEH, Jochimsen PR, Menck HR, Winchester DJ. An analysis of male and female breast cancer treatment and survival among demographically identical pairs of patients. Surgery 1999; 126: 775-781.

42) Eggemann H, Ignatov A, Smith BJ, Altmann U, von Minckwitz G, Röhl FW, Jahn M, Costa SD. Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 2013; 137: 465-470.

43) Reinisch M, Seiler S, Hauzenberger T, Schmatloch S, Strittmatter HJ, Zahm DM. Male-GBG54: a prospective, randomised, multi-centre, phase II study evaluating endocrine treatment with either tamoxifen +/– gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients. Presented at the 2017 San Antonio Breast Cancer Symposium, 2017.

44) Cardoso F, Costa A, Senkus E, Aapro M, André F, Barrios CH, Bergh J, Bhattacharyya G, Biganzoli L, Cardoso MJ, Carey L, Corneliussen-James D, Curigliano G, Dieras V, El Saghir N, Eniu A, Fallowfield L, Fenech D, Francis P, Gelmon K, Gennari A, Harbeck N, Hudis C, Kaufman B, Krop I, Mayer M, Meijer H, Mertz S, Ohno S, Pagani O, Papadopoulos E, Peccatori F, Penault-Llorca F, Piccart MJ, Pierga JY, Rugo H, Shockney L, Sledge G, Swain S, Thomssen C, Tutt A, Vorobiof D, Xu B, Norton L, Winer E. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 2017; 28: 16-33.

45) Doyen J, Italiano A, Largillier R, Ferrero JM, Fontana X, Thyss A. Aromatase inhibition in male breast cancer patients: biological and clinical implications. Ann Oncol 2009; 21: 1243-1245.

46) Masci G, Gandini C, Zuradelli M, Pedrazzoli P, Torrisi R, Lutman FR, Santoro A. Fulvestrant for advanced male breast cancer patients: a case series. Ann Oncol 2011; 22: 985.

47) de la Haba Rodríguez JR, Porras Quintela I, Pulido Cortijo G, Berciano Guerrero M, Aranda E. Fulvestrant in advanced male breast cancer. Ann Oncol 2009; 20: 1896-1897.

48) Agrawal A, Ayantunde AA, Rampaul R, Robertson JFR. Male breast cancer: a review of clinical management. Breast Cancer Res Treat 2007; 103: 11-21.

49) Helwick C. Is Male Breast Cancer Overlooked in Clinical Trials? The ASCO Post 2019.

50) Jaga K, Dharmani C. The epidemiology of pesticide exposure and cancer: a review. Rev Environ Health 2005; 20: 15-38.

51) Bounias M. Etiological factors and mechanism involved in relationships between pesticide exposure and cancer. J Environ Biol 2003; 24: 1-8.

52) Weichenthal S, Moase C, Chan P. A review of pesticide exposure and cancer incidence in the agricultural health study cohort. Environ Health Perspect 2010; 118: 1117-1125.

53) Natarajan R, Aljaber D, Au D, Thai C, Sanchez A, Nunez A, Resto C, Chavez T, Jankowska MM, Benmarhnia T, Yang JA, Jones V, Tomsic J, McCune JS, Sistrunk C, Doan S, Serrano M, Cardiff RD, Dietze EC, Seewaldt VL. Environmental exposures during puberty: window of breast cancer risk and epigenetic damage. Int J Environ Res Public Health 2020; 17: 493.

54) Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Altman DG, Booth A, Chan A-, Chang S, Clifford T, Dickersin K, Egger M, Gøtzsche PC, Grimshaw JM, Groves T, Helfand M, Higgins J, Lasserson T, Lau J, Lohr K, McGowan J, Mulrow C, Norton M, Page M, Sampson M, Schünemann H, Simera I, Summerskill W, Tetzlaff J, Trikalinos TA, Tovey D, Turner L, Whitlock E. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1.

55) Davis DL, Blair A, Hoel DG. Agricultural exposures and cancer trends in developed countries. Environ Health Perspect 1993; 100: 39-44.

56) Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 1993; 85: 648-652.

57) Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelman J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and asian women. J Natl Cancer Inst 1994; 86: 589-599.

58) Wiklund K, Dich J. Cancer risks among female farmers in sweden. Cancer Causes Control 1994; 5: 449-457.

59) Kettles MA, Browning SR, Prince TS, Horstman SW. Triazine herbicide exposure and breast cancer incidence: An ecologic study of Kentucky counties. Environ Health Perspect 1997; 105: 1222-1227.

60) Van 'T Veer P, Lobbezoo IE, Martín-Moreno JM, Guallar E, Gómez-Aracena J, Kardinaal AFM, Kohlmeier L, Martin BC, Strain JJ, Thamm M, Van Zoonen P, Baumann BA, Huttunen JK, Kok FJ. DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. Br Med J 1997; 315: 81-85.

61) López-Carrillo L, Blair A, López-Cervantes M, Cebrián M, Rueda C, Reyes R, Mohar A, Bravo J. Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: a case-control study from Mexico. Cancer Res 1997; 57: 3728-3732.

62) Hunter DJ, Hankinson SE, Laden F, Colditz GA, Manson JE, Willet WC, Speizer FE, Wolff MS. Plasma organochlorine levels and the risk of breast cancer. New Engl J Med 1997; 337: 1253-1258.

63) Olaya-Contreras P, Rodríguez-Villamil J, Posso-Valencia HJ, Cortez JE. Organochlorine expo-

sure and breast cancer risk in Colombian women. Cad Saude Publica 1998; 14: 125-132.

64) Petralia SA, Chow WH, McLaughlin J, Jin F, Gao YT, Dosemeci M. Occupational risk factors for breast cancer among women in Shanghai. Am J Ind Med 1998; 34: 477-483.

65) Fleming LE, Bean JA, Rudolph M, Hamilton K. Cancer incidence in a cohort of licensed pesticide applicators in Florida. J Occup Environ Med 1999; 41: 279-288.

66) Mendonça GAS, Eluf-Neto J, Andrada-Serpa MJ, Carmo PAO, Barreto HHC, Inomata ONK, Kussumi TA. Organochlorines and breast cancer: a case-control study in Brazil. Int J Cancer 1999; 83: 596-600.

67) Fleming LE, Bean JA, Rudolph M, Hamilton K. Mortality in a cohort of licenced pesticide applicators in Florida. Occup Environ Med 1999; 56: 14-21.

68) Ward EM, Schulte P, Grajewski B, Andersen A, Patterson DG, Turner W, Jellum E, Deddens JA, Friedland J, Roeleveld N, Waters M, Ann Butler M, Dipietro E, Needham LL. Serum organochlorine levels and breast cancer: a nested case-control study of Norwegian women. Cancer Epidemiol Biomarkers Prev 2000; 9: 1357-1367.

69) Band PR, Le ND, Fang R, Deschamps M, Gallagher RP, Yang P. Identification of occupational cancer risks in British Columbia: a population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. J Occup Environ Med 2000; 42: 284-310.

70) Aronson KJ, Miller AB, Wooleott CG, Sterns EE, McCready DR, Lickley LA, Fish EB, Hiraki GY, Holloway C, Ross T, Hanna WM, SenGupta SK, Weber JP. Breast adipose tissue concentrations of polychlorinated biphenyls and other organochlorines and breast cancer risk. Cancer Epidemiol Biomarkers Prev 2000; 9: 55-63.

71) Høyer AP, Jørgensen T, Grandjean P, Hartvig HB. Repeated measurements of organochlorine exposure and breast cancer risk (Denmark). Cancer Causes Control 2000; 11: 177-184.

72) Stellman SD, Djordjevic MV, Britton JA, Muscat JE, Citron ML, Kemeny M, Busch E, Gong L. Breast cancer risk in relation to adipose concentrations of organochlorine pesticides and polychlorinated biphenyls in long island, new york. Cancer Epidemiol Biomarkers Prev 2000; 9: 1241-1249.

73) Millikan R, Devoto E, Duell EJ, Tse CK, Savitz DA, Beach J, Edmiston S, Jackson S, Newman B. Dichlorodiphenyldichloroethene, polychlorinated biphenyls, and breast cancer among African-American and white women in North Carolina. Cancer Epidemiol Biomarkers Prev 2000; 9: 1233-1240.

74) Demers A, Ayotte P, Brisson J, Dodin S, Robert J, Dewailly E. Risk and aggressiveness of breast cancer in relation to plasma organochlorine concentrations. Cancer Epidemiol Biomarkers Prev 2000; 9: 161-166.

75) Duell EJ, Millikan RC, Savitz DA, Newman B, Smith JC, Schell MJ, Sandler DP. A population-based case-control study of farming and breast cancer in North Carolina. Epidemiology 2000; 11: 523-531.

76) Dolapsakis G, Vlachonikolis IG, Varveris C, Tsatsakis AM. Mammographic findings and occupational exposure to pesticides currently in use on Crete. Eur J Cancer 2001; 37: 1531-1536.

77) Janssens JP, Van Hecke E, Geys H, Bruckers L, Renard D, Molenberghs G. Pesticides and mortality from hormone-dependent cancers. Eur J Cancer Prev 2001; 10: 459-467.

78) Thomas JK, Qin B, Howell DA, Richardson BE. Environmental hazards and rates of female breast cancer mortality in Texas. Sociol Spectr 2001; 21: 359-375.

79) Mathur V, Bhatnagar P, Sharma RG, Acharya V, Sexana R. Breast cancer incidence and exposure to pesticides among women originating from Jaipur. Environ Int 2002; 28: 331-336.

80) Safi JM. Association between chronic exposure to pesticides and recorded cases of human malignancy in Gaza governorates (1990-1999). Sci Total Environ 2002; 284: 75-84.

81) Charlier C, Albert A, Herman P, Hamoir E, Gaspard U, Meurisse M, Plomteux G. Breast cancer and serum organochlorine residues. Occup Environ Med 2003; 60: 348-351.

82) Brody JG, Aschengrau A, McKelvey W, Rudel RA, Swartz CH, Kennedy T. Breast cancer risk and historical exposure to pesticides from wide-area applications assessed with GIS. Environ Health Perspect 2004; 112: 889-897.

83) O'Leary ES, Vena JE, Freudenheim JL, Brasure J. Pesticide exposure and risk of breast cancer: a nested case-control study of residentially stable women living on Long Island. Environ Res 2004; 94: 134-144.

84) Muir K, Rattanamongkolgul S, Smallman-Raynor M, Thomas M, Downer S, Jenkinson C. Breast cancer incidence and its possible spatial association with pesticide application in two counties of England. Public Health 2004; 118: 513-520.

85) Reynolds P, Hurley SE, Goldberg DE, Yerabati S, Gunier RB, Hertz A, Anton-Culver H, Bernstein L, Deapen D, Horn-Ross PL, Peel D, Pinder R, Ross RK, West D, Wright WE, Ziogas A; California Teachers Study. Residential proximity to agricultural pesticide use and incidence of breast cancer in the California Teachers Study cohort. Environ Res 2004; 96: 206-218.

86) Mills PK, Yang R. Breast cancer risk in hispanic agricultural workers in California. Int J Occup Environ Health 2005; 11: 123-131.

87) Raaschou-Nielsen O, Pavuk M, LeBlanc A, Dumas P, Weber JP, Olsen A, Tjønneland A, Overvad K, Olsen JH. Adipose organochlorine concentrations and risk of breast cancer among postmenopausal Danish women. Cancer Epidemiol Biomarkers Prev 2005; 14: 67-74.

88) Engel LS, Hill DA, Hoppin JA, Lubin JH, Lynch CF, Pierce J, Samanic C, Sandler DP, Blair A, Alavanja MC. Pesticide use and breast cancer risk among farmers' wives in the agricultural health study. Am J Epidemiol 2005; 161: 121-135.

89) Zumbado M, Goethals M, Álvarez-León EE, Luzardo OP, Cabrera F, Serra-Majem L, Domínguez-Boada L. Inadvertent exposure to organochlorine pesticides DDT and derivatives in people from the Canary Islands (Spain). Sci Total Environ 2005; 339: 49-62.

90) Alavanja MCR, Sandler DP, Lynch CF, Knott C, Lubin JH, Tarone R, Thomas K, Dosemeci M, Barker J, Hoppin JA, Blair A. Cancer incidence in the agricultural health study. Scand J Work Environ Health 2005; 31: 39-45.

91) Waliszewski SM, Bermudez MT, Infanzon RM, Silva CS, Carvajal O, Trujillo P, Arroyo SG, Pietrini RV, Saldaña VA, Melo G, Esquivel S, Castro F, Ocampo H, Torres J, Hayward-Jones PM. Persistent organochlorine pesticide levels in breast adipose tissue in women with malignant and benign breast tumors. Bull Environ Contam Toxicol 2005; 75: 752-759.

92) Rubin CH, Lanier A, Kieszak S, Brock JW, Koller KR, Strosnider H, Needham L, Zahm S, Harpster A. Breast cancer among Alaska native women potentially exposed to environmental organochlorine chemicals. Int J Circumpolar Health 2006; 65: 18-27.

93) Khanjani N, English DR, Sim MR. An ecological study of organochlorine pesticides and breast cancer in rural Victoria, Australia. Arch Environ Contam Toxicol 2006; 50: 452-461.

94) Teitelbaum SL, Gammon MD, Britton JA, Neugut AI, Levin B, Stellman SD. Reported residential pesticide use and breast cancer risk on long island, new york. Am J Epidemiol 2007; 165: 643-651.

95) Cohn BA, Wolff MS, Cirillo PM, Scholtz RI. DDT and breast cancer in young women: new data on the significance of age at exposure. Environ Health Perspect 2007; 115: 1406-1414.

96) Itoh H, Iwasaki M, Hanaoka T, Kasuga Y, Yokoyama S, Onuma H, Nishimura H, Kusama R, Tsugane S. Serum organochlorines and breast cancer risk in Japanese women: a case-control study. Cancer Causes Control 2009; 20: 567-580.

97) Jacome GPO, Koifman RJ, Monteiro GTR, Koifman S. Environmental exposure and breast cancer among young women in Rio de Janeiro, Brazil. J Toxicol Environ Health Part A Curr Iss 2010; 73: 858-865.

98) Xu X, Dailey AB, Talbott EO, Ilacqua VA, Kearney G, Asal NR. Associations of serum concentrations of organochlorine pesticides with breast cancer and prostate cancer in U.S. adults. Environ Health Perspect 2010; 118: 60-66.

99) Zota AR, Aschengrau A, Rudel RA, Brody JG. Self-reported chemicals exposure, beliefs about disease causation, and risk of breast cancer in the Cape Cod Breast Cancer and Environment Study: a case-control study. Environ Health Global Access Sci Sour 2010; 9: 40.

100) Farooq U, Joshi M, Nookala V, Cheriyath P, Fischman D, Graber NJ, Stellman SD, Muscat J. Self-reported exposure to pesticides in residential settings and risk of breast cancer: a case-control study. Environ Health Global Access Sci Sour 2010; 9: 30.

101) Waggoner JK, Kullman GJ, Henneberger PK, Umbach DM, Blair A, Alavanja MCR, Kamel F, Lynch CF, Knott C, London SJ, Hines CJ, Thomas KW, Sandler DP, Lubin JH, Beane Freeman LE, Hoppin JA. Mortality in the agricultural health study, 1993-2007. Am J Epidemiol 2011; 173: 71-83.

102) Ashley-Martin J, Vanleeuwen J, Cribb A, Andreou P, Guernsey JR. Breast cancer risk, fungicide exposure and CYP1A1*2a gene-environment interactions in a province-wide case control study in Prince Edward Island, Canada. Int J Environ Res Public Health 2012; 9: 1846-1858.

103) El-Zaemey S, Heyworth J, Fritschi L. Noticing pesticide spray drift from agricultural pesticide application areas and breast cancer: a case-control study. Aust New Zealand J Public Health 2013; 37: 547-555.

104) Holmes AK, Koller KR, Kieszak SM, Sjodin A, Calafat AM, Sacco FD, Varner DW, Lanier AP, Rubin CH. Case-control study of breast cancer and exposure to synthetic environmental chemicals among Alaska native women. Int J Circumpolar Health 2014; 73: 25760.

105) El-Zaemey S, Heyworth J, Glass DC, Peters S, Fritschi L. Household and occupational exposure to pesticides and risk of breast cancer. Int J Environ Health Res 2014; 24: 91-102.

106) Parrón T, Requena M, Hernández AF, Alarcón R. Environmental exposure to pesticides and cancer risk in multiple human organ systems. Toxicol Lett 2014; 230: 157-165.

107) Lerro CC, Koutros S, Andreotti G, Friesen MC, Alavanja MC, Blair A, Hoppin JA, Sandler DP, Lubin JH, Ma X, Zhang Y, Freeman LEB. Organophosphate insecticide use and cancer incidence among spouses of pesticide applicators in the agricultural health study. Occup Environ Med 2015; 72: 736-744.

108) Cohn BA, La Merrill M, Krigbaum NY, Yeh G, Park JS, Zimmermann L, Cirillo PM. DDT exposure in utero and breast cancer. J Clin Endocrinol Metab 2015; 100: 2865-2872.

109) Salerno C, Carcagnì A, Sacco S, Palin LA, Vanhaecht K, Panella M, Guido D. An italian population-based case-control study on the association between farming and cancer: are pesticides a plausible risk factor? Archiv Environ Occup Health 2016; 71: 147-156.

110) He TT, Zuo A-J, Wang J-G, Zhao P. Organochlorine pesticides accumulation and breast cancer: a hospital-based case-control study. Tumor Biol 2017; 39: 1010428317699114.

111) Wielsøe M, Kern P, Bonefeld-Jørgensen EC. Serum levels of environmental pollutants is a risk factor for breast cancer in Inuit: a case con-

trol study. Environ Health Global Access Sci Sour 2017; 16: 56.

112) Engel LS, Werder E, Satagopan J, Blair A, Hoppin JA, Koutros S, Lerro CC, Sandler DP, Alavanja MC, Beane Freeman LE. Insecticide use and breast cancer risk among farmers' wives in the agricultural health study. Environ Health Perspect 2017; 125: 097002.

113) Eldakroory SA, Morsi DAE, Abdel-Rahman RH, Roshdy S, Gouida MS, Khashaba EO. Correlation between toxic organochlorine pesticides and breast cancer. Hum Exp Toxicol 2017; 36: 1326-1334.

114) Chang S, El-Zaemey S, Heyworth J, Tang MC. DDT exposure in early childhood and female breast cancer: evidence from an ecological study in Taiwan. Environ Int 2018: 1106-1112.

115) Silva AMC, Campos PHN, Mattos IE, Hajat S, Lacerda EM, Ferreira MJM. Environmental exposure to pesticides and breast cancer in a region of intensive agribusiness activity in Brazil: a case-control study. Int J Environ Res Public Health 2019; 16: 3951.

116) Huang W, He Y, Xiao J, Huang Y, Li A, He M, Wu K. Risk of breast cancer and adipose tissue concentrations of polychlorinated biphenyls and organochlorine pesticides: a hospital-based case-control study in Chinese women. Environ Sci Pollut Res 2019; 26: 32128-32136.

117) Cohn BA, Cirillo PM, Terry MB. DDT and breast cancer: prospective study of induction time and susceptibility windows. J Natl Cancer Inst 2019; 111: 803-810.

118) Cohn BA, Cirillo PM, La Merrill MA. Correlation of body mass index with serum DDTs predicts lower risk of breast cancer before the age of 50: prospective evidence in the child health and development studies. J Expos Sci Environ Epidemiol 2019; 29: 302-309.

119) Cocco P, Figgs L, Dosemeci M, Hayes R, Linet MS, Hsing AW. Case-control study of occupational exposures and male breast cancer. Occup Environ Med 1998; 55: 599-604.

120) Fleming LE, Bean JA, Rudolph M, Hamilton K. Cancer incidence in a cohort of licensed pesticide applicators in Florida. J Occup Environ Med 1999; 41: 279-288.

121) Fleming LE, Bean JA, Rudolph M, Hamilton K. Mortality in a cohort of licensed pesticide applicators in Florida. Occup Environ Med 1999; 56: 14-21.

122) Fleming LE, Gómez-Marín O, Zheng D, Ma F, Lee D. National health interview survey mortality among US farmers and pesticide applicators. Am J Ind Med 2003; 43: 227-233.

123) Macfarlane GJ, Biggs A, Maconochie N, Hotopf M, Doyle P, Lunt M. Incidence of cancer among UK Gulf war veterans: cohort study. Br Med J 2003; 327: 1373-1375.

124) Villeneuve S, Cyr D, Lynge E, Orsi L, Sabroe S, Merletti F, Gorini G, Morales-Suarez-Varela M, Ahrens W, Baumgardt-Elms C, Kaerlev L, Eriksson M, Hardell L, Févotte J, Guénel P. Occupation and occupational exposure to endocrine disrupting chemicals in male breast cancer: a case-control study in Europe. Occup Environ Med 2010; 67: 837-844.

125) Parrón T, Requena M, Hernández AF, Alarcón R. Environmental exposure to pesticides and cancer risk in multiple human organ systems. Toxicol Lett 2014; 230: 157-165.

126) Sabarwal A, Kumar K, Singh RP. Hazardous effects of chemical pesticides on human health–Cancer and other associated disorders. Environ Toxicol Pharmacol 2018; 63: 103-114.

127) Kaur K, Kaur R. Occupational pesticide exposure, impaired DNA repair, and diseases. Indian J Occup Environ Med 2018; 22: 74-81.

128) Ledda C, Loreto C, Zammit C, Marconi A, Fago L, Matera S, Costanzo V, Sanzà GF, Palmucci S, Ferrante M, Costa C, Fenga C, Biondi A, Pomara C, Rapisarda V. Non-infective occupational risk factors for hepatocellular carcinoma: a review (review). Mol Med Rep 2017; 15: 511-533.

129) Manasa K, Chitra V. Phytoconstituents in the management of pesticide induced Parkinson's disease: a review. Biomed Pharmacol J 2019; 12: 1417-1424.

130) Rapisarda V, Ledda C, Matera S, Fago L, Arrabito G, Falzone L, Marconi A, Libra M, Loreto C. Absence of t(14;18) chromosome translocation in agricultural workers after short-term exposure to pesticides. Mol Med Rep 2017; 15: 3379-3382.

131) Kim K, Kabir E, Jahan SA. Exposure to pesticides and the associated human health effects. Sci Total Environ 2017; 575: 525-535.

132) Czajka M, Matysiak-Kucharek M, Jodłowska-Jędrych B, Sawicki K, Fal B, Drop B, Kruszewski M, Kapka-Skrzypczak L. Organophosphorus pesticides can influence the development of obesity and type 2 diabetes with concomitant metabolic changes. Environ Res 2019; 178: 108685.

133) Costa C, Rapisarda V, Catania S, Di Nola C, Ledda C, Fenga C. Cytokine patterns in greenhouse workers occupationally exposed to α-cypermethrin: an observational study. Environ Toxicol Pharmacol 2013; 36: 796-800.

134) Ledda C, Fiore M, Santarelli L, Bracci M, Mascali G, D'agati MG, Busà A, Ferrante M, Rapisarda V. Gestational hypertension and organophosphorus pesticide exposure: a cross-sectional study. Biomed Res Int 2015; 2015: 280891.

135) Pourhassan B, Meysamie A, Alizadeh S, Habibian A, Beigzadeh Z. Risk of obstructive pulmonary diseases and occupational exposure to pesticides: a systematic review and meta-analysis. Public Health 2019; 174: 31-41.

136) Mamane A, Baldi I, Tessier JF, Raherison C, Bouvier G. Occupational exposure to pesticides and respiratory health. Eur Respir Rev 2015; 24: 306-319.

137) Montana A, Rapisarda V, Esposito M, Amico F, Cocimano G, Nunno ND, Ledda C, Salerno M. A rare case of suicide by ingestion of phorate: a case report and a review of the literature. Healthcare 2021; 9: 131.

138) Mostafalou S, Abdollahi M. Pesticides: an update of human exposure and toxicity. Arch Toxicol 2017; 91: 549-599.

139) Ledda C, Cannizzaro E, Cinà D, Filetti V, Vitale E, Paravizzini G, Di Naso C, Iavicoli I, Rapisarda V. Oxidative stress and DNA damage in agricultural workers after exposure to pesticides. J Occup Med Toxicol 2021; 16: 1.

140) Vinceti M, Filippini T, Violi F, Rothman KJ, Costanzini S, Malagoli C, Wise LA, Odone A, Signorelli C, Iacuzio L, Arcolin E, Mandrioli J, Fini N, Patti F, Lo Fermo S, Pietrini V, Teggi S, Ghermandi G, Scillieri R, Ledda C, Mauceri C, Sciacca S, Fiore M, Ferrante M. Pesticide exposure assessed through agricultural crop proximity and risk of amyotrophic lateral sclerosis. Environ Health Global Access Sci Sour 2017; 16: 91.

141) Longnecker MP, Rogan WJ, Lucier G. The human health effects of DDT (dichlorodiphenyl-trichloroethane) and PCBs (polychlorinated biphenyls) and an overview of organochlorines in public health. Annu Rev Public Health 1997; 18: 211-244.

142) EPA. Endocrine disruptor screening program: what are endocrine disruptors? Endocrine Disruptor Screening Program: What are Endocrine Disruptors? 2001.

143) Soto AM, Sonnenschein C, Chung KL, Fernandez MF, Olea N, Olea Serrano F. The E-SCREEN assay as a tool to identify estrogens: an update on estrogenic environmental pollutants. Environ Health Perspect 1995; 103: 113-122.

144) Korach KS, Sarver P, Chae K, McLachlan JA, McKinney JD. Estrogen receptor-binding activity of polychlorinated hydroxybiphenyls: conformationally restricted structural probes. Mol Pharmacol 1988; 33: 120-126.

145) Kelce WR, Stone CR, Laws SC, Gray LE, Kemppainen JA, Wilson EM. Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist. Nature 1995; 375: 581-585.

146) IARC. IARC monographs on the evaluation of carcinogenic risks to humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 1994.

147) IARC. IARC monographs on the evaluation of carcinogenic risks to humans. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2018.

148) Chan M, Chang MC, González R, Lategan B, Del Barco E, Vera-Badillo F, Quesada P, Goldstein R, Cruz I, Ocana A, Cruz JJ, Amir E. Outcomes of estrogen receptor negative and progesterone receptor positive breast cancer. PLoS One 2015; 10.

149) Yu KD, Di GH, Wu J, Lu JS, Shen KW, Liu GY, Shen ZZ, Shao ZM. Breast cancer patients with estrogen receptor-negative/progesterone receptor-positive tumors: being younger and getting less benefit from adjuvant tamoxifen treatment. J Cancer Res Clin Oncol 2008; 134: 1347-1354.

150) Murphy CE, Carder PJ, Lansdown MRJ, Speirs V. Steroid hormone receptor expression in male breast cancer. Eur J Surg Oncol 2006; 32: 44-47.

151) Yue W, Yager JD, Wang JP, Jupe ER, Santen RJ. Estrogen receptor-dependent and independent mechanisms of breast cancer carcinogenesis. Steroids 2013; 78: 161-170.

152) Snedeker SM. Pesticides and breast cancer risk: a review of DDT, DDE and dieldrin. Environ Health Perspect 2001; 109: 35-47.

153) Gellert RJ, Heinrichs WL, Swerdloff RS. DDT homologues: estrogen-like effects on the vagina, uterus and pituitary of the rat. Endocrinology 1972; 91: 1095-1100.

154) López-Cervantes M, Torres-Sánchez L, Tobías A, López-Carrillo L. Dichlorodiphenyldichloroethane burden and breast cancer risk: a meta-analysis of the epidemiologic evidence. Environ Health Perspect 2004; 112: 207-214.

155) Fenton SE, Reed C, Newbold RR. Perinatal environmental exposures affect mammary development, function, and cancer risk in adulthood. Annu Rev Pharmacol Toxicol 2012; 52: 455-479.

156) Rudel RA, Fenton SE, Ackerman JM, Euling SY, Makris SL. Environmental exposures and mammary gland development: state of the science, public health implications, and research recommendations. Environ Health Perspect 2011; 119: 1053-1061.

157) Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. Environ Health Perspect 2003; 111: 389-394.

158) Fenton SE, Birnbaum LS. Timing of environmental exposures as a critical element in breast cancer risk. J Clin Endocrinol Metab 2015; 100: 3245-3250.

159) Pike MC, Spicer DV, Dahmoush L, Press MF. Estrogens, progestogens, normal breast cell proliferation, and breast cancer risk. Epidemiol Rev 1993; 15: 17-30.

160) Dehghan M, Baniasadi H, Fakhri Moghadam R, Salehi M. Cosmetic products don't increase the risk of breast cancer: a retrospective case-control study in southeast Iran. WCRJ 2020; 7: e1572.

161) Ebrahimzadeh E, Gholizadeh Pasha AR, Kamrani G, Yousefi T, Zahedian A, Tilaki KH, Qujeq D. Assessment of alpha-L-fucosidase and fucosyltransferase 4 enzymes in healthy and tumor tissues of patients with breast cancer. WCRJ 2020; 7: e1756.

162) Akbari Bazm M, Naseri L, Khazaei M. Methods of inducing breast cancer in animal models: a systematic review. WCRJ 2018; 5: e1182.

163) Bakhshi Aliabad H, Khanamani Falahati-Pour S, Ahmadirad H, Mohamadi M, Reza Hajizadeh M, Bakhshi G, Mahmoodi M. Vanadium complex induced apoptosis in HepG2 cells by the up-regulation of p53, p21, and Caspase-8. WCRJ 2019; 6: e1293.

164) Del Buono A, D'orta A, Tarro G, Rossi P, Papa S, Iodice L, Abbadessa A, Montano L, Portale G, Berretta M, Di Francia R. "Terra dei fuochi, the starting point". The role of prevention and complementary medicine in the clinical practice. WCRJ 2018; 5: e1112.