Occupational exposure and risk of breast cancer (Review)

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Abstract. Breast cancer is a multifactorial disease and the most commonly diagnosed cancer in women. Traditional risk factors for breast cancer include reproductive status, genetic mutations, family history and lifestyle. However, increasing evidence has identified an association between breast cancer and occupational factors, including environmental stimuli. Epidemiological and experimental studies demonstrated that ionizing and non-ionizing radiation exposure, night-shift work, pesticides, polycyclic aromatic hydrocarbons and metals are defined environmental factors for breast cancer, particularly at young ages. However, the mechanisms by which occupational factors can promote breast cancer initiation and progression remains to be elucidated. Furthermore, the evaluation of occupational factors for breast cancer, particularly in the workplace, also remains to be explained. The present review summarizes the occupational risk factors and the associated mechanisms involved in breast cancer development, in order to highlight new environmental exposures that could be correlated to breast cancer and to provide new insights for breast cancer prevention in the occupational settings. Furthermore, this review suggests that there is a requirement to include, through multidisciplinary approaches, different occupational exposure risks among those associated with breast cancer development. Finally, the design of new epigenetic biomarkers may be useful to identify the workers that are more susceptible to develop breast cancer.

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Abbreviations: PAH, polycyclic aromatic hydrocarbon; EMF, electromagnetic fields; IARC, International Agency for Research on Cancer; EDC, endocrine-disrupting chemical; UNSCEAR, United Nations Scientific Committee on the Effects of Atomic Radiation; PCB, polychlorinated biphenyl; OCP, organochlorines pesticide; DDE, dichlorodiphenyldichlroethylene; BaP, benzo[a]pyrene; OP, organophosphate; DDT, dichlorodiphenyltrichloroethane; AhR, aryl hydrocarbon receptor; AHH, aryl hydrocarbon hydroxylase; ERα, estrogen receptor α; SNP, single-nucleotide polymorphism; Cd, cadmium; Pb, lead; Cu, copper; Cr, chromium; Zn, zinc; Hg, mercury

Key words: breast cancer, occupational exposure, pesticides, metals, night-shift work, ionising radiation, benzene

Contents

1. Introduction

Breast cancer is the most commonly diagnosed cancer in women and the second worldwide cause of fatality among female patients, following lung cancer (1).

Although diagnostic, therapeutic and preventive improvements have been reached in the past, the incidence of breast cancer is still increasing in all countries, particularly those undergoing rapid changes in human development (2,3). Nearly 12% of women will experience invasive breast cancer in their lifetime, which equates to >20 million cases (4).

The lifetime risk of fatality from breast cancer is ~3.4%. The international incidence of female breast cancer varies markedly, being highest in the United States, Australia, New Zealand, Western and Northern Europe (incidence >80/100,000); intermediate in Southern and Eastern Europe and South America, and lowest in Asia and among African women living in sub-Saharan Africa (incidence ≤30/100,000) (5,6).

The wide range of female breast cancer mortality rates is less marked compared to variations in incidence, due to improved survival in high-income countries compared to low-and-middle-income countries (3).

A number of accepted risk factors for breast cancer include reproductive status, genetic mutations and family history; however, lifestyle, environmental or occupational features of breast cancer are not completely verified (7-9).

The International Agency for Research on Cancer (IARC) assessed the carcinogenicity of numerous substances, which could definitely or possibly produce breast cancer (10,11). According to the IARC classification (11), there are no agents with sufficient evidence in humans that can be classified as 'carcinogenic to humans' (group 1) to the human breast, which could be considered work related (6).

Exposure to night-shift work represents the most significant occupational risk associated with breast cancer and it has been

Table I. Search terms strategy for PubMed/Scholar.

Strategy	Search terms
1)	Breast cancer, mammary cancer, breast neoplasm, breast OR mammary tumor
2)	Occupation, occupational, work-related, workers, environmental, pollutants, occupational exposure OR risk
3)	Ionising radiation, non-ionising radiation, electromagnetic fields
4)	Endocrine disruptors, pesticides, organochlorine, DDT, organophosphates, carbamates, pyrethroids, disulfiram, parathion, malathion
5)	Combustion products, polycyclic aromatic hydrocarbon, PAH, benzene, benzo[a]pyrene, 1,1-dichloroethane, 1,2-Dichloroethane, 1,2-dichloropropane
6)	Night work, shift work, night-shift work
7)	Metals, cadmium, lead, nickel, metalloestrogen

PAH, polycyclic aromatic hydrocarbon; DDT, dichlorodiphenyltrichloroethane.

classified as a carcinogen by the IARC (10). Several studies among nurses have indicated that this population has a higher risk to develop breast cancer compared to the general female population, showing a close association between occupation and cancer development (12-14).

The IARC also established a strong association that exposure to ionizing radiation can increase the risk of breast cancer (15). Additionally, non-ionizing radiation, mainly electromagnetic fields (EMF) have been implicated in the pathogenesis of breast cancer in women and in men, suggesting an association between breast cancer and EMF that requires further evaluation (16).

Similarly, chemical substances such as ethylene oxide, polycyclic aromatic hydrocarbons (PAHs), perfluorooctanoic acid and different pesticides are investigated as carcinogenic factors for breast cancer in occupational settings (17,18). All these substances, known as endocrine-disrupting chemicals (EDCs), can alter endocrine processes and disrupt normal mammary tissue development, thus leading to adverse lifetime consequences (19). According to several studies, it is important to evaluate not only the time of exposure, mainly when the mammary gland is less differentiated and more sensitive, but also the effects which EDCs could produce at low doses of exposure (20,21).

Severe inhibitions of mammary development have only been observed in rodents at high EDC levels of exposure (19). These elevated doses may not be reached in humans except in rare cases of high occupational or non-occupational accidental exposures (such as pollution). The exact mechanisms for these changes remain to be elucidated; however, it was recently established that EDCs can alter the epigenome in cancers (22).

The aim of the present review was to carry out an update of the literature on the occupational risk factors involved in breast cancer development, in order to highlight new exposures that are correlated to breast cancer and to provide insight to the way researchers address breast cancer prevention in occupational settings.

2. Methods

In the present study, a PubMed/Scholar search was conducted in English journals for studies of breast cancer and occupational risk factors published in peer-reviewed journals. Search terms are summarized in Table I. References from included studies were checked. Accordingly, non-relevant and repeated literatures were excluded. All the abstracts were reviewed and the final set of studies was decided upon. Epidemiological and experimental studies, specifically analyzing occupational exposure and the risk of breast cancer, were included. Any restrictions with regard to place of origin or ethnicity of the women and men, or occupational settings were not placed. Studies of female breast cancer with ≤5 exposed women, and studies of male breast cancer with <1 observed or expected case were excluded. In addition, studies in which the exposed group was predominantly workers with <1 year employment were excluded. The main characteristics of selected epidemiological studies on occupational exposed workers are summarized in Table II.

3. Environmental exposure

General. Breast cancer is not a single disease with variable morphological features and biomarkers, but a group of molecularly distinct neoplastic disorders, as confirmed by numerous studies. Although there is a suggested protective effect of higher parity, lactation and other reproductive factors against the development of breast cancer, currently 5-10% of breast cancers are linked to hereditary syndromes, and other well-established risk factors represent 30% of cases. Thus, the risk of breast cancer is not only influenced by the reproductive history and the genetic background but is also thought to be affected by lifestyle factors and exposure to environmental and occupational contaminants (9,23).

An association between occupation and breast cancer was first described at the end of the eighteenth century, when Bernardino Ramazzini revealed a high frequency of breast cancer in nuns, possibly due to their abstinence from sex. Since then, numerous *in vivo* studies showed that certain chemicals used in occupational settings and, particularly, polybrominated biphenyls, PAHs, polychlorinated biphenyls (PCBs) and other EDCs, have a role in the development of female and male breast cancer (24).

Also *in vitro* studies demonstrated that environmentally persistent chemicals can determinate genetic damage,

Table II. Selected published studies of occupational risk factors and breast cancer risk.

Risk factor compound	Authors	Study design	Results	Occupation	(Refs.)
Ionising radiation	Mohan *et al*	Cohort	Significant association	Radiologic technologists	(29)
	Jartti *et al*	Cohort	Significant association	Physicians	(30)
	Doody *et al*	Cohort	Significant association	Radiologic technologists	(31)
Non-ionising radiation	McElroy *et al*	Case-control	Significant association	Various	(37)
	Coogan *et al*	Case-control	Significant association	Various	(16)
	Dosemeci and Blair	Cohort	Significant association	Telephone industry workers	(38)
	Kliukiene *et al*	Case-control	Significant association	Radio and telegraph operators	(39)
	Forssén *et al*	Case-control	No significant association	Various	(40)
OC pesticides	Band *et al*	Case-control	Significant association	Farmers	(58)
	Brophy *et al*	Case-control	Significant association	Various	(59)
OP and OC pesticides	Dolapsakis *et al*	Case-control	Significant association	Greenhouse workers	(63)
OP pesticides	Lerro *et al*	Cohort	Significant association	Pesticide applicators sposuses	(62)
PAHs	Petralia *et al*	Case-control	Significant association	Various	(81)
	Costantini *et al*	Case-control	Significant association	Shoes factory workers	(82)
	Walker *et al*	Cohort	No significant association	Laundry and dry cleaning workers	(83)
	Ruder *et al*	Cohort	No significant association	Dry-cleaning workers	(84)
	Band *et al*	Case-control	Significant association	Laundry and dry cleaning workers	(58)
Night-shift work	Davis *et al*	Case-control	Significant association	Night-shift workers	(88)
	Hansen	Case-control	Significant association	Night-shift workers	(89)
	Lie *et al*	Case-control	Significant association	Night-shift workers	(90)
	Hansen and Lassen	Case-control	Significant association	Night-shift workers	(91)
	Menegaux *et al*	Case-control	Significant association	Night-shift workers	(92)
	Wang *et al*	Case-control	Significant association	Night-shift workers	(86)
	Li *et al*	Case-control	No significant association	Night-shift workers	(93)
	Schernhammer *et al*	Cohort	Significant association	Night-shift workers	(94)
	Åkerstedt *et al*	Cohort	Significant association	Night-shift workers	(95)
	Schwartzbaum *et al*	Cohort	No significant association	Night-shift workers	(96)
	Pronk *et al*	Cohort	No significant association	Night-shift workers	(97)
	Lin *et al*	Meta-analysis	Significant association	Various	(98)
Metals	Cantor *et al*	Case-control	Significant association	Various	(111)
	Pollan and Gustavsson	Cohort	Significant association	Metal platers and coaters	(112)
	Rahim *et al*	Meta-analysis	No significant association	Various	(113)

OP, organophosphate; OC, organochlorine; PAHs, polycyclic aromatic hydrocarbons.

influence cell biological processes and enzymatic activity, or mimic hormone activity.

Thus far, the most well longest-established environmental risk factor of breast cancer is exposure to ionizing radiation. Furthermore, industrial compounds, such as PCBs and agricultural pesticides, have been suggested as risk factors for female breast cancer in several studies (18).

Ionizing radiation exposure. In 2000, the IARC classified X- and γ-radiation as carcinogenic agents with sufficient evidence in humans showing a correlation between heavy exposures to ionizing radiation and breast cancer development (15). In studies of the Japanese population exposed to radiation during the World War II, a statistically significant correlation was identified between female and male breast cancer risk and atomic bomb in survivors of atomic bombings. The risk was 4-fold greater in women <20 years old at the time of the bombing (25,26).

The UNSCEAR reports conclude that there is a considerable evidence for the effects of ionizing radiation exposure on breast cancer rates, with a linear dose-response association (27). The elevated mortality rates for breast cancer are correlated to greater occupational exposures to ionizing radiation until 1950 compared to more recent times. A previous study demonstrated

the potential health consequences of occupational exposure to ionizing radiation in the medical professions, where breast cancer was more frequently diagnosed compared to other types of cancer (28). Mohan *et al* (29) evaluated the mortality risks resulting from exposure to low-dose ionizing radiation in a cohort of 146,022 US radiological technologists (73% women) and identified an elevated risk of fatality from breast cancer among women first employed prior to 1940 compared to those first employed in 1960 or later. Mortality risk was higher among female workers who first operated with fluoroscopy before 1950 compared to those who first were involved in these procedures later.

Jartti *et al* (30) conducted a cohort study on 1,312 Finnish physicians and observed a slightly elevated risk of breast cancer among physicians occupationally exposed to ionizing radiation in Finland compared to other physicians.

In a study based on a cohort of 56,436 U.S. female radiological technologists, Doody *et al* (31) evaluated incident breast cancer risks from 1983 to 1998 according to employment characteristics. The study demonstrated that the breast cancer incidence was elevated significantly for those women who began working before 1940 and in women who began working at ages <17 years. In a recent review and analysis, occupation as an airline flight personnel has been linked to increased female breast cancer risk in a number of studies. There is uncertainty regarding risk factors, nevertheless increased exposures to cosmic (atmospheric) ionizing radiation could contribute to the increased breast cancer incidence among flight workers (11).

Radiation increases the risk of breast cancer, by directly producing DNA damage and by altering common cellular and intracellular functions. Exposure to ionizing radiation could also enhance breast cancer development by indirectly influencing the ability of hormones or other chemical substances (32).

Recent genetic data indicate that women with certain gene mutations that may increase their susceptibility to develop breast cancer (such as ATM, TP53 and BRCA1/2) may be particularly at risk to the cancer-inducing effects of ionizing radiation exposure (33,34).

Molecular biology studies have shown that genes involved in DNA repair and sensitive to radiation exposure are associated with an increased breast cancer risk. Women with mutated forms of BRCA1 and BRCA2 share an ~80% chance of developing breast cancer during their life (18).

Few studies evaluated the combined role of genetic polymorphisms (such as ATM, TP53 and BRCA1/2) and exposure to ionizing radiation in the etiology of breast cancer in humans; as the genetic mutation or polymorphism of interest is typically extremely rare, additional studies are required to address whether common polymorphisms in DNA repair genes modify the effects of low-dose radiation exposure from medical sources (35).

Thus, it can be concluded that during the early nuclear years, high levels of exposure were recorded for a large number of workers in medical diagnostics, nuclear power industry and in the military, and more recent exposures can be considered to be much lower due to the recognition of the long-term health effects and the introduction of health prevention.

EMF. Although not all epidemiological or occupational studies demonstrate that exposure to EMF can cause breast cancer, some of these reported evidence for an increase of the risk following exposure to EMF. IARC classified exposure to low frequency EMF as 'possibly carcinogenic to human', however, the evidence for breast cancer is considered inadequate (36).

A recent case-control study in the US on women who were exposed to low, medium or high EMF levels in their workplace, reported that occupational exposure to EMF may be linked to a slight elevation in breast cancer risk (37).

Several studies have observed an increased risk of breast cancer among female radio and telegraph operators exposed to radiofrequency (1 type of EMF) and extremely low frequency EMF, and in women employed in the telephone industry. Notably, premenopausal women appear to be at a higher risk compared to post-menopausal women (16,38,39).

By contrast, a large case-control study, based on the Swedish population registers, found no evidence of an elevated risk of breast cancer associated with women working in occupations with high EMF exposures (40).

Although mechanisms underling the association between breast cancer and exposure to EMFs are not fully understood, several studies have reported that exposure to EMFs is important for women with estrogen-receptor positive breast tumors, particularly for premenopausal women who produce high levels of estrogens (41-43).

According to several studies, exposure to EMFs may inhibit the synthesis of melatonin by the pineal gland and/or depress the levels of this hormone. As a result, increased circulating levels of estrogens and consequently enhanced proliferation of breast tissue cells have been observed (44,45). *In vitro* and *in vivo* studies confirmed this hypothesis by demonstrating the inhibition of the hormone production in blood rats exposed to EMFs, as well as the suppression of mammary tumorigenesis by melatonin (46). However, other studies have not suggested inhibition of melatonin generation in humans mediated by EMFs exposure (47). Additional research is required on this topic to establish the effect of EMFs on initiating breast cancer.

Pesticides. Pesticides constitute a heterogeneous category of chemicals specifically designed for preventing, destroying, repelling or mitigating any pest (48).

Numerous groups of pesticides can be classified and can be grouped according to the target organisms (such as insecticides, fungicides and herbicides), chemical structure (such as organochlorine, organophosphorus, phenoxy acid herbicides, urea and pyrethroids), or type of health hazard produced (49). The association between pesticide exposure and cancerogenesis is actually one of the main issues in occupational and environmental toxicology.

Numerous pesticides have shown carcinogenicity of varying levels. They have also been reported as genotoxic, tumor promoters, immunotoxic and estrogenic (50). As an endocrine disruptor, the pesticide can mimic the actions of different hormones (estrogen or testosterone); thus, it can produce an increase in estrogen-related physiological responses. The pesticide can also behave like an antagonist by binding to the estrogens receptors; thereby, the normal physiological responses associated with estrogen stimulation of its receptor do not occur. Furthermore, the pesticide may interfere with the synthesis, transport, metabolism or elimination of estrogen, causing either an increase or decrease in estrogenic

effects. Regardless, the normal homeostasis of the system will be disrupted (4).

The class of compounds that has been identified in the past as the most significant chemical agent associated with female cancers includes the organochlorines (OCPs), chlorinated hydrocarbons that are frequently used as pesticides, insecticides or herbicides (19).

The OCPs can persist for extended periods in the environment and in the body; they are detected in the food supply and breast milk, and can be stored in the adipose tissue of animals and humans. Furthermore, they can act like both estrogen agonists and antagonists in several animal experiments (51). Therefore, a possible correlation between breast cancer risk and organochlorine exposure has been hypothesized and investigated over the past decades (52); however, no consistent evidence has been found to support the hypothesis (53,54).

These incongruities may be due to various factors, including biological matrices used to estimate exposure and target samples, with highly varied historical and current pesticide exposure levels and distinct ethnicities, age groups and/or dietary characteristics (55).

Although the majority of OCPs have been banned from use in almost all the industrialized countries, some, such as dichlorodiphenyltrichloroethane (DDT), are the best investigated. There are a few OCPs still in use (endosulfan, lindane and dicofol), which have been associated to several diseases, including breast cancer.

Although there were numerous studies that reported a weak elevation in the levels of DDT and the incidence of breast cancer, none were statistically significant. Rural populations of agricultural works and their families who may be exposed to higher doses of OCPs, such as DDT, compared to the general population, have been reported to have a higher incidence of breast cancer compared to the populations not exposed. Retrospective studies have produced conflicting results due to certain limits, such as small sample size, difficulty in measuring pesticide exposure, and correlating blood pesticide levels to the progression of breast cancer (4).

Cohn *et al* (56) investigated whether serum *p*,*p*'-DDT and *o*,*p*'-DDT are associated with breast cancer, using blood samples obtained prior to the banning of DDT and when the use of this pesticide was extremely high. These results are consistent with the hypothesis that *p*,*p*'-DDT exposure in life was retained longer, possibly due to slower metabolism, and may increase the breast cancer risk.

In a study of a population from the Canary Islands (Spain), Boada *et al* (57) demonstrated that an organochlorine pesticide mixture, including aldrin, *p*,*p*'-DDE and dichlorodiphenyldichloroethane, could have a relevant role in breast cancer development.

Band *et al* (58) identified a significant association in the combined group of pre- and post-menopausal women, notably in crop farmers and in fruit and vegetable farming.

Brophy *et al* (59), in an exploratory population-based case-control study, identified an elevated risk for developing breast cancer in the agricultural population, suggesting the importance for evaluating environmental risk factors and detailed occupational histories of cancer patients.

Other classes of popular pesticides have replaced OCPs over the years in a continuing search for less toxic, but effective, agents. Organophosphates (OPs) were formerly among the most widely used household pesticides, representing ~22% of non-agricultural usage in 2001 (50).

Malathion and diazinon are probably carcinogenic to humans (group 2A), and dichlorvos, parathion and tetrachlorvinphos are classified as possibly carcinogenic to humans (group 2B) (60); parathion is considered as 'a possible human carcinogen' by the US Environmental Protection Agency (61). An increased cancer risk has been associated with several OP insecticides in epidemiological studies; however, the majority of studies on OP use and cancer outcomes have largely been conducted in predominantly male populations. Consequently, little is known regarding the potential impact of personal OP use among women, specifically on the development of female cancers, despite the fact that OPs as a class are thought to have endocrine-disrupting properties (62). This is possibly due to the fact that male workers are more engaged in pesticide handling compared to female subjects (48).

However, in a preliminary study, Dolapsakis *et al* (63) evaluated whether occupational exposure to pesticides in greenhouses (mainly OPs and organocarbamates) may enhance the risk of malignant or premalignant findings in mammographic examination. The study concluded that women exposed to pesticides may have higher risks of incidence for a number of lesions, which are risk markers for subsequent invasive breast cancers. Recently, possible evidence of chlorpyrifos estrogenicity has been reported (64).

In a study aimed to prospectively examine the use of OP insecticides and risk of multiple cancer sites among women, associations with several cancer sites were observed, including thyroid, ovary and breast. The increased risks that they observed for hormonally-related cancers are consistent with the hypothesis that OPs may act as endocrine disruptors, although additional studies exploring this and other possible mechanisms are required (62).

Carbamates are another class of widely used insecticides. Carbaryl has been classified as a group III carcinogenic (unclassifiable as to human carcinogenicity) from the IARC (65). Carbamates could inhibit 17b-estradiol and progesterone activity in human breast and endometrial cancer cells (66). Recently, the carbamate fungicide benomyl has been reported as a risk factor for breast cancer by acting as an endocrine disruptor (67).

Synthetic pyrethroids, some of the most common pesticides in current use, have been investigated for their potential estrogenic activity; thus it has been demonstrated that this class of pesticide may contribute to produce breast cancer in human cells (68,69).

Although the majority of studies on carcinogenesis agree upon the fact that pesticides can cause breast cancer acting like endocrine disruptors, recent evidence also suggest that their adverse effects may be associated with the interactions with the aryl hydrocarbon receptor (AhR), a transcription factor that regulates xenobiotic metabolism enzymes that belong to the cytochrome P450 1A family (including CYP1A1 and CYP1B1 enzymes). Thereby, it is considered as a mediator of toxicity during environmental pollutant metabolism. Long-term exposure to pesticides could activate AhR and the estrogen receptor, which may affect the expression of genes regulated by the AhR-ER crosstalk, thus producing

an imbalance between CYP1A1 and CYP1B1 enzymes. This mechanism could lead to the accumulation of DNA adducts and represent a potential initial factor involved in mammary carcinogenesis (70). According to L'Héritier *et al* (70), genes involved in the aforementioned crosstalk could become important biomarkers to evaluate potential long-term effects of pesticides on breast cancer.

PAHs. PAHs are ubiquitous environmental pollutants that are generated primarily through incomplete combustion of carbon-containing materials, including coals, crude oil, wood, gasoline, foods and cigarettes (71). Therefore, higher exposures to PAHs occur among selected occupations, such as firefighters and coke oven, aluminium and foundry workers [Knower *et al* (22)].

Substantial epidemiological evidence suggests that long-term exposure to PAH-rich emissions is associated with a higher lung cancer risk in exposed workers (IARC 2005) (71). However, the carcinogenic properties of PAHs in human breast cancer remain to be elucidated. Using PAH-DNA adducts as a body burden measure of exposure and response, epidemiological studies have observed a positive association with breast cancer among women (72).

In 1996, Li *et al* (73) evaluated aromatic DNA adducts in normal adjacent tissues from 87 breast cancer patients and in normal tissues of 29 reduction mammoplasty non-cancer controls. A significantly higher level of aromatic DNA adducts was identified in adjacent breast tissues of cancer patients compared to non-cancer controls, supporting the hypothesis that environmental carcinogen exposure may contribute to human breast cancers.

PAH-DNA adducts reflect short-term exposures, whereas breast cancer is believed to develop over a number of years (74). Thus, it is of interest to evaluate longer-term PAH exposures in association with breast cancer risk. In 2015, Mordukhovich *et al* (75) observed positive associations between vehicular traffic-related benzo[a]pyrene (BaP) exposure and breast cancer incidence among women with comparatively high long-term traffic BaP exposures, although effect estimates were imprecise.

Gene-specific methylation of RARβ, and perhaps APC, may interact with PAH-DNA adducts to increase risk of hormone receptor-positive breast cancer. There was little evidence that adducts were associated with or interacted with other methylation markers of interest (76).

In a small-scale, case-control study of breast cancer, Li *et al* (77) made several interesting and important observations, such as a high level of *in vitro* BaP-induced DNA adducts was a significant risk factor for breast cancer; environmental carcinogen exposure may modify individual susceptibility to carcinogen exposure and in turn the risk of breast cancer. When breast tissues were exposed *in vitro* to a classic tobacco carcinogen, BaP, women with breast cancer exhibited a significantly higher level of BaP-DNA adducts compared to the healthy controls. Following adjustment for several confounding factors, the level of BaP-induced DNA adducts was identified as a significant risk factor for breast cancer. As all the tissue samples were exposed to the same level of BP under the same experimental conditions, the level of DNA adducts detected in the present study reflects intrinsic factors that determine the tissue response to such damage, such as carcinogen metabolism and DNA repair capacities. The higher level of DNA damage among cases thus suggests that cases had an elevated activation, deficient detoxification and reduced DNA repair capacity compared with controls (77).

PAHs metabolism occurs in the liver by cytochrome P450 (such as CYP1A1), which could activate the aryl hydrocarbon hydroxylase (AHH). Genotypic variants of CYP1A1 can improve increased AHH function. Several studies suggest that women with the variant genotype(s) have a higher risk to develop breast cancer compared to women with the normal genotype (8).

Rundle *et al* (78) reported that the null variant of the detoxifying gene GSTM1 was associated with adduct levels in cases, but not in controls. These results suggest that the GSTM1 polymorphism has a role in the formation of PAH-DNA adducts, thus preventing accumulation of environmental damage in breast tissue.

Benzene is chemical solvent involved in several hematological diseases, such as leukemia and myelodysplastic syndrome (79). Experimental studies demonstrated that exposure to benzene can induce breast cancer (80). However, few studies on humans have shown that benzene is involved in breast cancer development. A case-control study by Petralia *et al* (81) suggested an association between breast cancer risk and occupational exposure to benzene in women. In addition, Costantini *et al* (82) conducted an epidemiological cohort study of female workers using benzene-based glues in a shoe factory in Italy. The study demonstrated that chronic exposure to benzene can be one of the risk factor for breast cancer.

Further studies also examined the role of several solvents, such as 1,1-dichloroethane, 1,2-dichloroethane, 1,2-dichloropropane, dichloromethane and tetrachloroethylene, which are commonly used in industrial settings. However, the majority of the studies did not report substantial results (83,84). Recently, Band *et al* (58) observed a 4.9-fold increased risk of breast cancer among postmenopausal women employed in laundry and dry cleaning.

Night-shift work. In 2007, an expert group of the IARC, based on strong animal and weak human evidence, classified night-shift shift work as a possible cause of breast cancer (group 2A) (10). In Scandinavia, where the association between breast cancer and night-shift work appears to be an issue, numerous studies have been carried out (85); however, there were also certain studies that did not report any association, possibly due to differences in night-shift work evaluation, study design, recall bias and incomplete adjustment for confounding factors (86).

Nurses and flight personnel represent 2 of the main occupational populations investigated in epidemiological studies of night-shift work. Otherwise, few studies referred to the general population (87).

The epidemiological evidence of an association between shift work and breast cancer risk among women is based on case-control and cohort studies; some of them identified a positive association, however, others reported no association. A positive correlation between shift work and breast cancer risk was described in several case-control studies, which highlighted that the breast cancer risk is associated with

characteristics of night work, and provided new evidence that night work may have a role in the occurrence of the disease (88-92). More recently, in 2015, a positive correlation between breast cancer risk and night-shift work was reported by Wang *et al* (86). In particular, the combined effects of night-shift work with no daytime napping or longer sleep duration are greater compared to the independent effects. By contrast, Li *et al* (93) showed a negative correlation between shift work and breast cancer risk in the Chinese population, suggesting that the effect of shift work on breast cancer development may be different in Asian and Caucasian women.

Schernhammer *et al* (94) performed 2 large prospective cohort studies to assess the risk of breast cancer among nurses following their rotating night-shift work. The study demonstrated that the risk of breast cancer was statistically significantly elevated in postmenopausal women who worked for ≥30 years on rotating night-shifts, compared with those who never worked rotating night-shifts. Among premenopausal women an increased breast cancer risk of 23% after 1-14 years of shift work was observed. Additionally, the results of a recent study showed a significant association between exposure to night work for >20 years and breast cancer in women who were followed up to the age of 60 years (95). By contrast, different results were reported by Schwartzbaum *et al* (96) and by Pronk *et al* (97). These studies did not identify any evidence for an association between shift work and breast cancer incidence rates.

Recently, a meta-analysis of prospective cohort studies supports the idea that there is a positive dose-effects association between night-shift work and morbidity of breast cancer (98).

In order to explain the mechanisms involved in breast cancer development and potentially associated carcinogenic effects of circadian rhythm disruption, a variety of mechanisms has been suggested (99).

According to mechanistic hypotheses, exposure to light at night suppresses the nocturnal peak of melatonin and the circadian master clock, while sleep disruption produces negative effects on the immune system. All these factors could cause asynchronous cell proliferation of breast tissue (100).

The first suggestion that the globally increasing use of electric lighting at night may alter melatonin homeostasis and contribute to the breast cancer development was made in 1987 by Stevens (11,99).

Melatonin may act on initiation, promotion and progression of tumors. A decrease of melatonin production favors an upregulation of the gonadal axis, thus causing an increased in circulating levels of estrogens, which is a well-known risk factor for breast cancer. Additionally, melatonin can activate the glutathione antioxidative pathways. Furthermore, melatonin acts as a response modifier to estrogens: i) Exerts an anti-estrogenic effect with interaction with estrogen receptor α (ERα); ii) counteracts the effect of estradiol on breast cancer cell proliferation, invasiveness and telomerase activity; iii) downregulates the expression of protein growth factors and the proto-oncogenes stimulated by estrogens; and iv) downregulates the human epidermal growth factor receptor 2 (HER2/neu) (101).

Recently, a genetic variation in the genes involved in the circadian rhythm pathway has been an important topic of debate. Several studies have also examined genetic variants in circadian genes associated with the breast cancer risk, but only the core circadian genes and a limited number of single-nucleotide polymorphisms (SNPs) in each gene were evaluated in epidemiological studies (102,103). Furthermore, it has been hypothesized that genetic polymorphisms in the circadian pathway genes can increase the risk of breast cancer among women working at night (104). In a recent study by Truong *et al* (100), the analysis of individual SNPs showed a strong association between breast cancer and rs11932595 in *CLOCK* and rs1482057 in *RORA* genes in postmenopausal women, but not in in premenopausal women. The study suggested that circadian genes may have a role in breast cancer etiology. However, further studies are required in order to clarify the role of specific combination of SNPs of the circadian rhythm pathway in breast cancer development.

Metals. A number of heavy metals are naturally present in the environment in small concentrations; however, as a consequence of their increased use in several occupational settings, heavy metals can be considered as environmental contaminants (105).

The main global sources of anthropogenic contamination by heavy metals include different industrial places, such as power industry, transport, municipal waste management, waste dumping sites, fertilizers and waste used to fertilize soil. Emission of heavy metals into the environment occurs through a wide range of processes and pathways, including to the air (such as combustion, extraction and processing), to surface water (through direct deposition, runoff and releases from storage and transport), and to the soil (and hence into crops and other organisms through the food chain) (106).

It is also generally accepted that some of these metals are essential for living organisms in small quantities, but toxic in higher concentrations or in other speciation forms, including copper (Cu), chromium (Cr), manganese and zinc (Zn), while metabolic roles have been demonstrated for others, such as cadmium (Cd), mercury (Hg) and lead (Pb), which are considered as obligatory toxic. Numerous heavy metals appear to be involved in the development of several types of cancer (including arsenic, beryllium, Cd, nickel and hexavalent Cr), acting like potential endocrine disruptors or metalloestrogens (4).

Metalloestrogens are small ionic metals and metalloids that can function as endocrine disruptors by mimicking the action of estrogens. Two different classes of metalloestrogens can be distinguished: The first includes oxyanions, arsenite, antimony, nitrite, selenite and vanadate; the second consists of bivalent cations, including Cd, calcium, cobalt, Cu, nickel, Cr, Pb, Hg and tin. Metalloestrogens can activate the estrogen receptor in the absence of estradiol; thus exposure to these metals may increase the risk of developing breast cancer. In support of this hypothesis, environmental exposure to a number of the metalloestrogens is widespread and has increased significantly over the last 50-60 years. The majority of the metalloestrogens also have a long biological half life (for example, Cd has a half life of 10-30 years) and accumulate in the body and in the mammary tissue.

There are several studies that support the idea that exposure to Cd is linked to an increased risk of developing breast cancer (107). Cd is a widespread metallic element occurring in the environment naturally (such as volcanic activity, weathering of Cd-containing rocks and sea spray) and as a pollutant

deriving from industrial (such as batteries, coatings and plastic stabilizers), agricultural (such as contamination of phosphate fertilizers) and other sources (such as release from motor vehicle fuel combustion and tire wear) (108).

Evidence obtained from *in vivo* and *in vitro* studies strongly suggests that Cd can act like a metalloestrogen, binding itself to ERα (with an equilibrium dissociation constant nearly equivalent to that of estradiol), activate it, and induce expression of certain ER target genes (109). Additionally, Cd produces other estrogen-like effects, including increased uterine weight; changes in uterine lining; increased epithelial cell density in mammary glands; increased cell proliferation; and increased aneuploidy (110).

In a study by Cantor *et al* (111), using a case-control method, mortality records from 24 American states were used to evaluate occupational exposures as a possible cause of breast cancer. The death certificates were coded for occupation and industry. Following adjustment for several confounding factors, associations for probability and level of exposure were found for several metals/metal oxides, in particular workplace exposure to Cd was associated with an 8-20% increase in the breast cancer risk among Caucasian women and a 50-130% increase in the risk among African-American women.

A second epidemiological study in a retrospective cohort of working Swedish women also suggests a link between occupational exposure to Cd and an increased risk of breast cancer. In this study, women employed as metal platers and coaters and exposed to Cd exhibited a significant excess risk to develop breast cancer (112). Although these epidemiological studies suggest a link between Cd and breast cancer, more experimental and epidemiological studies are required in order to establish a cause-effect association between exposure to Cd and development of the disease.

In a recent meta-analysis on 13 studies including 978 exposed cases and 1,279 controls, several reviewed evidence suggesting that exposure to Cd is a cause of breast cancer. The results indicated that the frequencies of breast cancer were not significantly higher in the Cd-exposed group compared to the controls; thus, exposure to Cd could not significantly induce the breast cancer (113).

Similar to Cd, nickel is able to bind to ERα, promote cell proliferation and induce aneuploidy. However, further studies at the animal, cellular, and molecular levels are required to demonstrate whether and how low-dose, chronic nickel exposure can lead to breast cancer. As much less is known regarding the nickel-binding site compared to the Cd-binding site on ERα, more structural studies are necessary as well to confirm the role of nickel as a metalloestrogen (105).

Certain metal elements, such as Zn, iron, Cu, Cr and Pb, can cause proliferation of malignant cells in breast cancer development. The resulting destabilization of the genetic material cause the synthesis of mutant p53 protein, the block of apoptosis and regulatory effects of cells. This can lead to tumor progression and the destabilization of the genome, which is represented by increased DNA fragmentation (114).

4. Conclusions

Breast cancer is a complex multifactorial disease, from its initiation to its progression. Current literature is not unanimous regarding the specific clinical and pathological characteristics of breast cancer possibly linked to occupational settings. In addition, there are no molecular biomarkers that can be used specifically to identify occupational exposures associated with breast cancer. These exposures may be mediated by environmental factors, such as lifestyle (diet, alcohol consumption and smoking habits), work-correlated features (including shift work), and other individual conditions. Although there are a number of experimental studies on the ability of several compounds to cause breast tissue development in rodent models, there are few published studies that have demonstrated cancer development in humans. The assessment of the exposures should possibly consider the short window of time when the structures of the gland are more sensitive.

As breast cancer is a multifactorial disease, the evaluation of occupational factors is hardly considered in the overall risks assessment and there is a requirement to include them in occupational hazard and risk assessments by a multidisciplinary investigation and interdisciplinary cooperation. Experimental models may be developed in order to evaluate interactions between lifestyle factors, such as circadian rhythms, diet and physical activities, and occupational exposure that may provide critical information on human variability, which is also dependent on epigenetic reprogramming. Therefore, the development of environmental epigenetic biomarkers may be more suitable for the prediction of future disease risk, including that for breast cancer.

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