Women's health and night shift work: Potential targets for future strategies in breast cancer (Review)

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Abstract. Breast cancer is the leading cause of cancer-associated amongst women worldwide. Several studies have shown that individual, environmental and occupational factors can serve an important role in the onset of breast cancer; although the majority of studies have demonstrated this association, and several studies have investigated the biological pathways, it is impossible to describe with certainty the causal relationship that involve circadian rhythm disruption and melatonin dysregulation with the oncogenic processes. Over the years, due to the introduction of more effective screening tools, an increase in the incidence of breast cancer as well as a decrease in the age at diagnosis has been witnessed. Subsequently, an increasing number of individuals have obtained care at a younger age, which has meant that after surgery and chemotherapy, these workers have had to return to work. In light of these paradigmatic changes, the aim of the present review was to identify potential targets for future organisational strategies that should be adopted in the workplace by occupational physicians, both for prevention and for the return-to-work process of working women who have suffered from breast cancer.

Contents

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1. Introduction

Breast cancer (BC) is the leading cause of cancer-associated amongst women worldwide. Considering the most updated data on BC from 2020, 2.261.419 new cases of BC were registered worldwide (accounting for 24.5% of all tumours in women). Of these, 531,086 cases (25.8%) in Europe were detected, with 55,133 new diagnoses (28.1%) in Italy (1).

BC is a multifactorial disease; however, the different risk factors established for pathological development do not fully explain the aetiology of the disease. The results of several studies showed that individual, environmental and occupational factors serve a critical role in the onset of this pathology (2-6). In women, the most common individual risk factors causing hereditary BC are genetic mutations involving the BRCA1 or BRCA2 genes. However, there are also less common inherited mutations in other genes, including ATM, TP53, CHEK2, PTEN, CDH1, STK11 and PALB2 (7). Lifestyle is an important risk factor, with lack of physical activity, excessive consumption of alcohol, a high body mass index (BMI), a high-fat diet and smoking all increasing the risk (2,8-11). Ethnicity, age and socio-economic status can influence the risk of developing BC. White women exhibit the highest incidence of BC, followed by Black, Asian and Hispanic women. This could be explained by racial and socioeconomic barriers to early detection and screening, and unequal access to treatment, as well as differences in lifestyles (12-16). Other individual factors are attributable to procreative aspects, such as the onset of menarche and menopause, as well as the age of first pregnancy with breastfeeding (17-19). Last but not least, a familiar BC and/or general predisposition to cancer may represent important risk factors (17,18), such as chronic fatigue, sleep disturbance and depression (20-22). Several studies have investigated the gene-environment interactions showing that BC risk is related to the common susceptibility variants, which can be altered by environmental factors, such as industrial air pollutants, soil or water contamination due to heavy metals and genotoxic agents, active or passive tobacco smoke (3,10,23-34). Finally, several occupational factors can expose workers to a higher risk of BC due to toxic compounds or exposure to ionising radiation, rotating night shifts or higher-status occupations (35-42).

This last association between BC and occupational factors is a topical issue, since it is estimated that exposure to occupational hazards causes up to 8% of cancers (37,43,44).

According to data from the seventh European Working Conditions Survey in 2020, 13 and 15% of female workers, in Italy (ITA) and European Union (EU) respectively, declared exposure to chemical products or substances for at least 25% of the time in the workplace. Moreover, 10% (ITA) and 14% (EU) of women stated they worked ≥1 time a month at night, whereas 18% (ITA) and 21% (EU) declared to perform work shifts (45).

Occupational exposure to rotating or night shifts could lead to the onset of tumours such as BC (46,47). In fact, in 2019, the International Agency for Research on Cancer (IARC) published a monograph that considered the relationship between night shift work and carcinogenesis. Based on both epidemiological and experimental scientific contributions on animals, the IARC Working Group defined night shift work, which causes an alteration of circadian rhythms, as a probable human carcinogen, with classification 2A (limited scientific evidence in humans, but sufficient evidence in animals) (48).

Although the results of the latest studies are controversial, the main pathogenetic hypothesis is based on the impact that night shift work and night light exposure could have on the rhythmicity of the circadian biological functions (49,50). These alterations result in disturbance of circadian rhythms, reduction of melatonin production and sleep perturbation, affecting several metabolic and physiological processes, including hormone synthesis and cell cycle progression (51-54).

Amongst the several mechanisms proposed to determine the effects of artificial light at night on BC, the majority seem to highlight the importance of inhibition of melatonin secretion during the night due to sleep deprivation, resulting in chronodisruption (55). In women performing shift or night work, melatonin secretion is inhibited by light, resulting in an increase in estrogen, since it has a significant anti-estrogenic activity (54,56).

This multifaceted hypothesis may explain why night workers may have a greater risk of developing BC compared to the general population (42,52,55,57) and why work organisations should implement a strategic procedure to prevent BC. Under these premises and also in light of the new evidence, this review aims to provide an overview of the most relevant risk factors, providing recommendations to fill gaps in risk assessment and suggest novel organisational strategies that occupational physicians should adopt in the workplace, both for the prevention and return-to-work process of female workers affected by BC.

2. Literature search

The review was performed by searching PubMed, Scopus and Web of Science databases. The inclusion criteria were: Full-text studies, published in English, published between 2015-2021, and studies associating BC risk with occupational factors, particularly shift and night work. Certain studies, although methodologically sound, were excluded as they were considered irrelevant to the purpose of the study. Most articles were found using the terms: 'breast cancer' AND 'night shift' OR 'breast cancer' AND 'night shift work' OR 'breast cancer' AND 'occupational exposure' OR 'breast cancer' AND 'occupational risk'. No restrictions were applied to the country of origin or ethnicity of the patients recruited. Furthermore, based on titles and abstracts, the relevance of the topic and admissibility of all the retrieved publications were further assessed. Finally, further relevant studies were identified through manual screening of the selected articles' reference lists and recently published reviews.

3. Mechanistic pathways

Shift work and melatonin secretion. Although the literature is controversial, as summarized in Table I, numerous studies have suggested that shift work and the night shift may represent one of the main occupational risks associated with BC (35,36,52,58).

Cordina-Duverger *et al* (59) analysed five case-controlled studies (Australia, Canada, France, Germany and Spain) by pooling the data into a single standardised dataset, demonstrating that night work amplified the risk of BC in women in premenopause, especially in those with a high frequency of night work, measured as the number of nights per week, and a long period of exposure. Amongst premenopausal women, the risk of BC was higher in recent night workers [odds ratio (OR)=1.41; 95% confidence interval (CI), 1.06-1.88] than in those who had stopped night work more than 2 years earlier (59). Similarly, women who worked at night showed an increased risk of developing BC when compared to women who never worked nights in Mexico (OR=8.58; 95% CI, 2.19-33.8) (49), as well as in Poland (OR=2.61; 95% CI, 1.94-3.53) (46). However, there was only a slight increase in higher BC risk amongst night shift workers in the Sister Study, with a cohort of 50,884 women who had a sister with breast tumour, but were BC-free themselves (60). Moreover, in a study conducted in Canada, Levin's equation was applied to assess attributable population fractions (PAFs) amongst women who worked night or rotating shifts in 1961-2000. The PAFs varied from 2.0-5.2, and 38% of overall incident BC cases in 2011 were detected in women who worked in health-related occupational environments (61). Nevertheless, this increased risk was observed in two prospective cohorts (5,971 in the Nurses' Health Study and 3,570 in the Nurses' Health Study 2, performed in USA), which showed an association between a high risk of BC and long-term night shift work (35). Conversely, in a study conducted on Korean women (62), and another study based on the Generations Study cohort (63) demonstrated the lack of association between night shift work and an increased risk of developing BC.

The causal links between night work and BC have yet to be established, although a plausible biological mechanism could be related to night light-related disruption of the circadian rhythm. The inhibition of night melatonin secretion along with sleep deprivation and chronodisruption is suggested to be a crucial mechanism by which artificial light at night could contribute to BC development (55).

However, even with regard to this proposed mechanism, the studies have shown contested results; a case-controlled study performed in Vancouver found no association between nocturnal artificial light and BC (64); whereas a case-controlled study performed in China (65) and a population-based case-controlled study in Spain (66) both

Table I. Summary of the main studies reviewed.

First author, year	Country	Time span	Study type	Result	(Refs.)
Jung *et al*, 2016	Not available	6-18 Years	Pooled analysis of 20 prospective cohort studies	Alcohol intake was positively associated with risk of overall BC, ER+, ER-, PR+ and PR- BC.	(11)
Ma *et al*, 2020	Not available	Not available	Bioinformatic analysis	Two lncRNAs (AL139280.1 and AP000851.1) and three mRNAs (MT1M, HBB and TFPI2) were identified as differential risk biomarkers in patients with BC in both the young and old age groups.	(12)
Barcenas *et al*, 2010	Not available	1990-2005	Systematic review	Black women had a significantly poorer overall survival risk compared with white women.	(14)
Wieder *et al*, 2016	United States of America	1973-2011	Retrospective study	African American race was demonstrated to be an independent predictive variable for decreased survival compared to the Caucasian race in women with a diagnosis of localized BC.	(15)
Taheri *et al*, 2019	Iran	Not available	Retrospective study	No significant relationship between the metastasis and recurrence of BC with age of patients and education levels.	(16)
Beral *et al*, 2002	30 countries	Not available	Pooled analysis of 47 epidemiological studies	The relative risk of BC was reduced by 4.3% for each year of breastfeeding, in addition to a reduction of 7.0% for each birth.	(17)
Johansson *et al*, 2013	Italy	1998-2002	Double-blind, placebo-controlled trial	Low-dose tamoxifen exhibited a positive outcome on the hormonal profile and fenretinide was associated with a weak anti-aromatase action, supporting the administration of low-dose tamoxifen or fenretinide as single agents in the prevention of BC in at-risk women.	(18)
Kröz *et al*, 2017	Germany	2011-2013	Cohort study	The study showed the effectiveness of a multimodal approach in the treatment of chronic cancer-related fatigue compared to the standard aerobic therapy.	(20)
Tsaras *et al*, 2018	Greece	2017	Cross-sectional study	Patients with BC were high risk for developing psychiatric disorders, such as depression and anxiety.	(21)
Fox *et al*, 2020	United States of America	2000-2010	Prospective study	Sleep disturbances and cancer-related fatigue are the most common symptoms associated with BC and its treatment, in particular chemotherapy.	(22)
Cohn *et al*, 2019	United States of America	1959-1967	Prospective study	DDT was associated with BC development. The risk was dependant on the timing of first exposure and diagnosis age. DDT appears to act as endocrine disruptor with responsive breast targets from *in utero* to menopause.	(27)

Table I. Continued.

First author, year	Country	Time span	Study type	Result	(Refs.)
Filippini *et al*, 2020	Not available	Not available	Meta-analysis	Limited evidence of an association between cadmium and BC.	(29)
Wegrzyn *et al*, 2017	United States of America	Since 1976	Cohort study	Long-term rotating night-shift work was associated with a higher risk of BC, particularly amongst women who performed shifts during young adulthood.	(35)
Fagundo-Rivera *et al*, 2020	Not available	2010-2020	Systematic review	Significant associations between BC and prolonged rotating night shifts.	(36)
Videnros *et al*, 2019	Sweden	1991-1996	Prospective cohort study	Occupational exposure to chemicals was associated with an elevated risk of BC. A minor increase in risk was seen after exposure to organic solvents. Statistically significant elevation of risk after >10 years of exposure to diesel exhaust was found.	(37)
Lee *et al*, 2019	Canada	2005-2010	Multicentre Study	Prolonged occupational exposure to polycyclic aromatic hydrocarbons may increase BC risk, especially amongst women with a family history of BC.	(39)
Schubauer-Berigan *et al*, 2015	United States	2002-2005	Cohort study	Increased BC incidence in a cohort of flight attendants compared to the general population. This incidence was not related to cosmic radiation or to circadian rhythm disruption.	(40)
Szkiela *et al*, 2020	Poland	2015-2019	Case-control study	The study supported the hypothesis that night shift work is a significant risk factor for BC.	(46)
Gómez-Salgado *et al*, 2021	Spain	Up to 2020	Cross-sectional study	The number of years worked, nights worked throughout life, and years working >3 nights per month were identified as significant risk variables for BC. The risk increased with other factors, such as sleep disturbance, physical stress or family responsibilities.	(47)
Bustamante-Montes *et al*, 2019	Mexico	Not available	Case-control study	The risk for BC increased amongst the women who performed night-work, even after adjusting for potential confounders.	(49)
Xiang *et al*, 2019	United States of America	Not available	*In vitro* study	Circadian disruption of melatonin by dim light at night increased resistance to Paclitaxel via epigenetic mechanisms.	(51)
Erdem *et al*, 2017	Norway	1990-2007	Case-control study	Telomere shortening was associated with the duration and intensity of night work, and may be a contributing factor for BC risk amongst female shift workers.	(52)
Erdem *et al*, 2017	Norway	1990-2007	Case-control study	Epigenetic regulation of CLOCK, BMAL1, CRY1 and PER1 may have contributed to BC in shift workers.	(53)

Table I. Continued.

First author, year	Country	Time span	Study type	Result	(Refs.)
El-Benhawy *et al*, 2021	Egypt	Not available	Case-control study	Nightshift workers had significantly lower levels of melatonin and total antioxidant capacity, and higher levels of serum inflammatory markers and cortisol than the control group. Workers occupationally exposed to ionizing radiation had significantly higher levels of serum melatonin, malondialdehyde and inflammatory markers, lower levels of serum cortisol and lower total antioxidant capacity than day shift workers.	(57)
Rosa *et al*, 2019	Not available	2005-2016	Systematic review	Shift work is a risk factor for stress, sleep disorders, metabolic disorders, diabetes, cardiovascular disorders and BC.	(58)
Cordina-Duverger *et al*, 2018	Not available	Up to 2016	Meta-analysis	Night shift work increases the risk of BC in pre-menopausal women, particularly those with high intensity and long duration of exposure.	(59)
Sweeney *et al*, 2020	Not available	2003-2009	Prospective cohort study	There was little evidence that rotating shift work or work at night was associated with a higher risk of BC.	(60)
Pahwa *et al*, 2019	Canada	1961-2000	Prospective cohort study	An estimated 2.0-5.2% of newly diagnosed BC cases in 2011 in Canada were attributable to shift work. This corresponds to 470-1,200 incident cases of BC.	(61)
Pham *et al*, 2019	Korea	2012-2018	Case-control study	No association between night shift work and the risk of BC was identified.	(62)
Jones *et al*, 2019	United Kingdom	2003-2014	Cohort study	The lack of overall association with dose, duration, and intensity of night shift, does not support an increased risk of BC from night shift work in women.	(63)
Ritonja *et al*, 2020	Canada	2005-2010	Population-based case-control study	No association between residential outdoor light at night and BC. Light at night has a small or no effect on BC risk.	(64)
Yang *et al*, 2019	China	2013-2016	Case-control study	Light exposure at night, habitual timing of sleep, night/shift work and frequency of night-time wakes were associated with an increased risk of BC. Sleep duration, sleep quality, sleep medication use, insomnia frequency and daytime nap were not associated with the risk of BC.	(65)
Garcia-Saenz *et al*, 2018	Spain	2008-2013	Case-control study	Prostate cancer and BC were associated with high estimated exposure to outdoor light at night in the blue-enriched light spectrum.	(66)
Lacerda *et al*, 2019	Not available	Not available	*In vitro* study	Melatonin was able to increase the expression levels of miR-148a-3p and decreased the gene and protein expression levels of IGF-1R and VEGF, both *in vitro* and *in vivo*. Melatonin also showed an inhibitory effect on the survival, migration and invasion of BC cells.	(67)

Table I. Continued.

First author, year	Country	Time span	Study type	Result	(Refs.)
Rajabi *et al*, 2020	Not available	Not available	*In vitro* study	Melatonin was able to attenuate DLL4 expression in estrogen-responsive BC cells and was able to induce apoptosis.	(68)
El-Sokkary *et al*, 2019	Not available	Not available	*In vitro* study	Melatonin and Taxol decreased cell migration and invasion at low doses. Melatonin may assist in preventing BC metastasis through inhibiting a DJ-1/KLF17/ID-1 signalling axis. The combination of melatonin and Taxol was a potent combination for management of BC metastasis.	(69)
Liu *et al*, 2020	Not available	Not available	*In vitro* study	Melatonin regulated BC progression via a lnc010561/miR-30/FKBP3 axis, which exhibited anticancer properties.	(70)
Salamanca-Fernández *et al*, 2018	Not available	Up to 2017	Systematic review	In this systematic review, 62.5% studies found an association between night shift work and increased risk of BC and prostate cancer. The evidence of a possible association between night-shift work and BC risk remains contested though.	(72)
Dun *et al*, 2020	Not available	Up to 2019	Systematic review and meta-analysis	Cancer risk was not significantly elevated with the increased light exposure of night-shift work.	(73)
Yuan *et al*, 2018	Europe, North America, Asia, and Australia	Up to 2016	Meta-analysis	Confirmed the positive association between night shift work and the risks of several common types of cancer in women, including BC. Cancer risk was increased with as the number of years of night shift work accumulated.	(74)
de Castro *et al*, 2018	Brazil	Not available	Case-control study	Melatonin serum levels were lower in patients with BC and in nurses working at night. Higher levels of melatonin and of a metabolite of oxidative metabolism (acetyl-N-formyl-5-methoxykynurenamine) were related with the clinical pathological characteristics of the patients with BC, such as metastasis and lymph node positive status, suggesting a relationship with the inflammatory response.	(77)
Vaughn *et al*, 2018	United States	Up to 2013	Population-based case-control study	The association of sleep quality differed by menopausal status, where mild sleep disturbance was associated with higher BC mortality in premenopausal women.	(82)
McNeil *et al*, 2020	Canada	2004-2008	Cohort study	No associations were found between shift work or sleep duration on the risk of breast and colorectal cancer.	(83)
Shi *et al*, 2013	Denmark	1993-1997	Cohort study	Long-term night shift work exposure may lead to the downregulation of miR-219, which may in turn lead to the downregulation of antitumor activity, thus increasing BC risk.	(88)

Table I. Continued.

First author, year	Country	Time span	Study type	Result	(Refs.)
Pham *et al*, 2019	Korea	2012-2017	Hospital-based case-control study	Night shift work increased risk of BC in women who harboured the heterozygote genotype of CRY2 rs2292912 or carried at least one minor allele of RORA rs1482057.	(90)
Carugno *et al*, 2019	Italy	Not available	Cross-sectional study	Night shift workers were associated with estrogen receptor 1, TP53 and BRCA1 hypomethylation. Telomere length was decreased in workers who had worked night shifts for >12 years.	(91)
Leensen *et al*, 2017	Netherlands	2011-2015	Longitudinal prospective intervention study	Return to work of patients with cancer was higher after completion of the multidisciplinary rehabilitation program.	(99)

BC, breast cancer; ER, estrogen receptor; PR, progesterone receptor; lncRNA, long non-coding RNA; DDT, dichloro-diphenyl-trichloroethane. CLOCK, Circadian Locomotor Output Cycles Kaput; BMAL1, Brain and Muscle ARNT-Like 1; CRY1, cryptochrome circadian regulator 1; PER1, Period Circadian Regulator 1; miR, microRNA; IGF-1R, insulin-like growth factor 1 receptor; VEGF, vascular endothelial growth factor; DLL4, δ-like 4; DJ-1, Protein deglycase DJ-1; KLF17, Krueppel-like factor 17; ID-1, DNA-binding protein inhibitor ID-1; FKBP3, FK506-binding protein 3; RORA, RAR-related orphan receptor α.

4. Risk assessment and prevention strategies

In work schedules characterized by night shifts, the occupational physicians can play a key role both in risk assessment and in prevention strategies. In particular, when workers susceptible to BC are employed, healthcare professionals can provide strategic contributions for primary prevention, health promotion and return to work. Primary prevention has different targets, such as adequately assessing the suitability for shift work, organising shifts according to ergonomic criteria, and adopting adequate compensatory measures to avoid significant disturbances in circadian rhythms, accumulation of sleep loss and conflicts in social life. Although certain pathologies can constitute a handicap for rotating or night work, shift work cannot and must not be a discriminatory criterion for selecting workers. Particularly, for female workers, more stressful living conditions can arise in relation to time pressures caused by the conflict between irregular working hours and habitual domestic commitments, especially for those women who are married and with children. Conversely, it may be the specific family conditions and/or economic needs that force several women to accept shift or night work. However, it is clear that there is no optimal or best shift pattern, so each shift scheme must be planned and adopted, taking into account the specific working conditions, the peculiar requirements of the tasks, and the particular individual and social characteristics of the workers. The occupational physician should evaluate individual health conditions, which could be related to or aggravated by shift work, to exempt workers from shift work or at least from the night shifts. It is also necessary that helpful information and suggestions should be given to workers on how to best cope with shift and night work, particularly concerning sleep, diet, stress control and good physical health.

Regarding the organization of work schedules, it is advisable to reduce night work by adopting rapid rotation schemes to limit the number of consecutive night shifts as much as possible, reducing the interference on circadian rhythms and sleep. In fact, it is suggested to prefer the rotation of shifts in 'phase delay' (Morning/Afternoon/Night), which supports the natural biological circadian rhythms, interspersed by at least 11 h intervals between one shift and the next, in order to allow improved recovery from any sleep loss and fatigue.

The occupational physician can also implement health promotion programs targeting the primary individual risk factors, promoting healthy lifestyle behaviours, for example supporting the introduction of a Mediterranean diet, that has been shown to be associated with a lower risk of BC incidence in women (94,95). The typical Mediterranean diet nutrients have shown a positive influence on the expression of inflammatory biomarkers, oxidative stress, DNA damage and genetic modifications, all aspects that can affect BC outcomes (96,97). Moreover, lifestyle modifications can positively impact BC survival, whose lower health-related quality of life negatively affects treatment compliance and disease outcomes (98).

Occupational physicians should encourage BC screening programs in female workers at risk of BC. It is well established that inclusion into mammography screening programs can result in earlier detection, showing a decrease in the rate of mastectomies, favouring breast conservation surgery. Therefore, BC screening programs are associated with re-employment; in fact,

showed that there was an increased risk of BC associated with exposure to night light, in particular, with external light in the blue spectrum.

To better understand the association between night work, the disruption of the circadian rhythm and the risk of BC, several studies investigated the role of the genes involved in the circadian pathway and melatonin regulation (51,67-71). However, both the relationship between circadian rhythm and genetic expression/modification and specific markers continues to be debated (50,72-75).

Moreover, melatonin is also a powerful antioxidant, due to its capacity to scavenge free radicals and stimulate antioxidative enzymes (76). Lower levels of melatonin were observed in patients with BC, suggesting that working at night modifies the circulating levels of biomarkers associated with inflammation and redox reactions (57,77).

Neuroendocrine disruption. In women employed in shift or night work, melatonin secretion, which has anti-estrogenic activity, is inhibited by light, resulting in a rise in estrogen levels (56). It is well known that early menarche, late menopause and no pregnancies, all factors linked to sex hormones exposure, are associated with an increased risk of BC (78). Sleep deprivation, resulting in shift work disorder, characterised by excessive sleepiness and sleep disturbances (79), has a strong influence on the neuro-immune-endocrine axis, which can affect cell proliferation and immune responses, including cytokine production (80) and some plasma metabolites, that may play an essential role in the circadian system (81). In particular, Daly *et al* (8) described a 16% increase in the incidence of BC in women aged 25-49 since 1990s, which may be at least partly attributed to more improved screening programs and detection methods, as well as changing lifestyles, highlighting the role of the endocrine factors in the onset of BC. In fact, younger women (<40 years) seem to be affected by more aggressive phenotypes of BC, resulting in a higher mortality rate. Moreover, young women were more likely to exhibit advanced disease stage tumours (larger size, lymph node involvement, poorly differentiated). Still, women aged <40 years seem to have a higher frequency of familiar history of BC, with a higher frequency of pathogenic mutations in the BC genes (BRCA1, BRCA2, TP53 and PALB2) compared with women with BC that develops after the age of 40, thus mutation penetrance appears higher in younger patients (8).

Regarding the relationship between poor sleep quality and BC, it is impossible to give a straightforward interpretation. In general, sleep disturbances are likely to be associated with aggressive subtypes of BC, as demonstrated by the Western New York Exposures and Breast Cancer study (82), conducted on a sample of 1,122 subjects with incident BC. This investigation also showed that sleep quality, well-known to be influenced by occupational features (42), is also linked to the state of menopause. However, no association was found between BC risk and sleep duration, sleep quality, use of sleep medication, frequency of insomnia and daytime napping in a case-controlled study conducted in China (65). This research showed that night shift work and frequency of nocturnal awakenings were associated with an increased risk of BC independently from menopausal status and tumour estrogen receptor status. Conversely, research on 21,804 participants from Alberta's Tomorrow project evaluated the primary effects of shift work and sleep duration on cancer incidence, and found no association between shift work or sleep duration and BC risk (83).

Disruption of circadian genes. Changes in the expression of circadian genes can be attributed to genetic or epigenetic mechanisms. Certain genes [Brain and Muscle ARNT-Like 1 (Bmal1), Period Circadian Regulator (Per)1 and Per2] have been hypothesized to act as tumour suppressors (84,85). Primary epigenetic controls are represented by DNA methylation and the modifications of histones (86). Altered expression of genes associated with the circadian rhythm is associated with atypical cell proliferation, impairment of DNA repair systems and apoptosis, the response to DNA damage, and an increase in drug resistance in human cancer cells (85). A previous study observed that mice with a shorter circadian cycle showed hypermethylation in the promoters of cryptochrome circadian regulator 1 (Cry1) and Per2 genes and hypomethylation in the Circadian Locomotor Output Cycles Kaput (CLOCK) promoter (87).

Several studies have demonstrated that lifestyle and circadian disruption are associated with changes in microRNA expression, such as miR-127, miR-146b and miR-219. These altered miRNA profiles may then lead to epigenetic modifications, supporting the hypothesis that long-term night shift work may increase BC risk (88,89).

A study conducted on Korean women investigated 22 polymorphisms in 11 genes in 941 cases of BC and 959 controls. In the analysis of single nucleotide polymorphisms, a correlation between night shift work and BC was found; specifically, night shift exposure increased the risk of BC in women carrying the heterozygous genotype of CRY2 rs2292912 or carrying at least one minor allele of RORA rs1482057 (90). Epigenetic changes in 5-methyl cytosine in five circadian genes, BMAL1, CLOCK, CRY1, PER1 and PER2, were also analysed in a population of night shift female nurses (278 BC cases, 280 controls). The authors suggested that epigenetic alteration of CLOCK, BMAL1, CRY1 and PER1 may contribute to BC in night shift workers. An Italian study found that night shifts were associated with ESR1, TP53 and BRCA1 hypomethylation in female nurses. |Further analysis showed that these night shift-associated markers could be of potential interest in the study of cellular ageing, genomic variability and cancer development (91). In another case-controlled study amongst Norwegian nurses, intensity and length of night work were associated with telomere shortening, which may contribute to an increased risk of BC amongst women working in shifts (52).

Bracci *et al* (92) evaluated alterations in BRCA expression in shift workers, finding lower levels of BRCA1 and BRCA2 in shift workers than in day workers, suggesting a potential role associated with a higher risk of BC (92).

In a murine model of spontaneous mammary carcinogenesis, authors noticed that mixed-background mice (B6*FVB PyMT:Luc2) developed BC within 10-12 weeks of age, and demonstrated that the circadian rhythm disruption considerably enhanced cancer-cell dissemination and pulmonary metastasis, and affected the immunosuppressive response showing the role of circadian dysregulation on breast tumour progression (93).

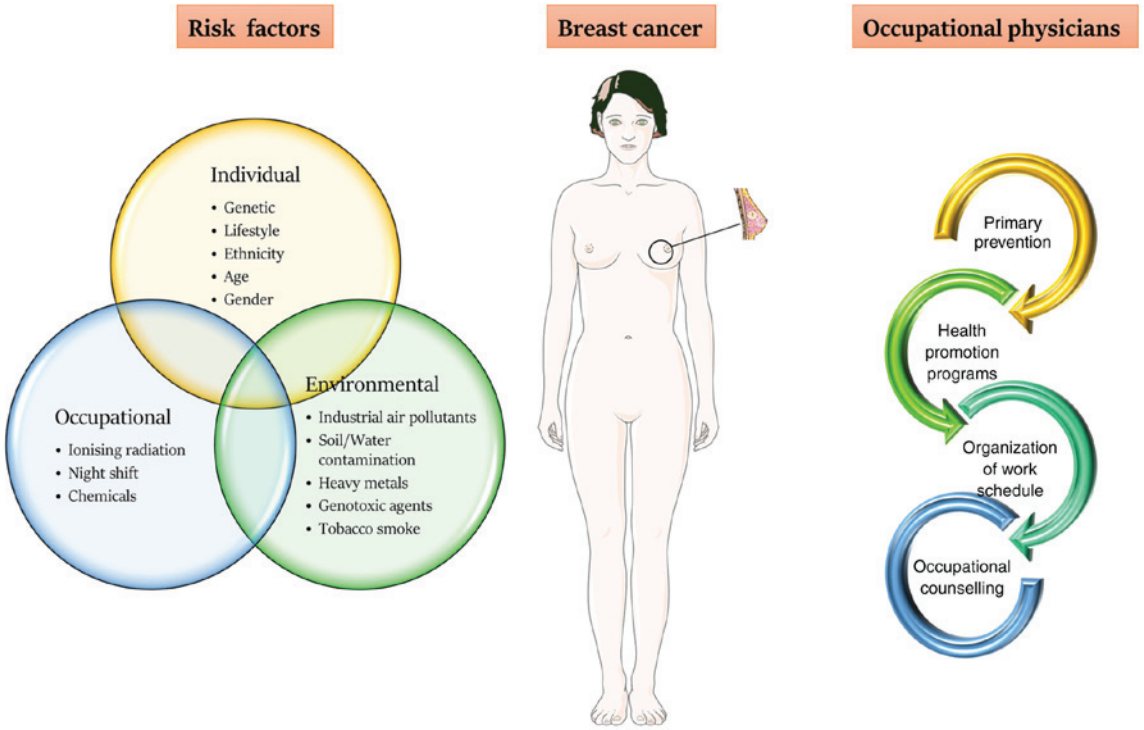

Figure 1. Interaction between individual, environmental and occupational risk factors in the development of breast cancer, as well as the role of the occupational physician.

an early diagnosis is frequently followed by a more efficient recovery and improved ability to work. After BC curative treatment, the assessment of a patient's ability to return to work should consider the following: Clinical outcomes, lifestyle and occupational variables. After the sick leave period, employer support to simplify the employee rehabilitation has been associated with a positive return to work experience. A rehabilitation program that combines occupational counselling, physical workout programs and physiotherapy during chemotherapy resulted in an increased return rate to work, improved quality of life and better ability to work (99). In this setting, the role of occupational physicians is crucial in informing workers on the benefits of rehabilitation plans, healthy lifestyles and assistances guaranteed by the law. A virtuous occupational physician should collaborate with the employer to adjust individual risk assessment and optimize tailored calibration of work tasks (Fig. 1).

5. Conclusions

The current review focused on the contribution of the occupational physician to the prevention and management of BC in the workplace, with a brief overview of the main individual, environmental and occupational risk factors associated with BC, which may have synergistic effects towards the susceptibility, development and progression of BC.

The overall examination of the reviewed contributions does not allow to exclude that exposure to shift and night work is related to an increased risk of developing BC; moreover, it leads to the hypothesis that this relationship is supported by both a theoretical background and possible pathogenetic mechanisms.

Though further studies are needed to establish a causal link, this review suggests introduction of a novel approach to management, including screening tools in the workplace, especially targeting those workers with greater exposure to shift or night work.

In this context, the role of the occupational physician is crucial in primary prevention, health promotion and in the return to work process. In particular, this return to work phase should take into consideration a multidisciplinary approach, involving employers adopting working features tailored on the specific worker's conditions.

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Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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