Research Article

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The relationship between night shift work and breast cancer incidence: A systematic review and meta-analysis of observational studies

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Abstract: The purpose of this study was to investigate the relationship between night shift work and breast cancer (BC) incidence. A search was performed in PubMed, EBSCO, Web of Science, and Cochrane Library databases before June 2021. The exposure factor of this study is night shift work, the primary outcome is the risk of BC. A total of 33 observational studies composed of 4,331,782 participants were included. Night shift work increases the risk of BC in the female population (hazard ratio [HR] = 1.20, 95% confidence interval [CI] = 1.10–1.31, p < 0.001), especially receptor-positive BC, including estrogen receptor (ER)+ BC (HR = 1.35, p < 0.001), progesterone receptor (PR)+ BC (HR = 1.30, p = 0.003), and human epidermal growth factor receptor 2 (HER2)+ BC (HR = 1.42, p < 0.001), but has no effect on HER2− BC (HR = 1.10, p = 0.515) and ER-/PR− BC (HR = 0.98, p = 0.827). The risk of BC was positively correlated with night shift working duration, frequency, and cumulative times. For women who start night work before menopause, night work will increase the incidence of BC (HR = 1.17, p = 0.020), but for women who start night work after menopause, night work does not affect BC (HR = 1.04, p = 0.293). Night work can increase the incidence of BC in the female population. The effect of long working hours, frequency, and the cumulative number of night shifts on BC is influenced by menopausal status.

Keywords: breast cancer, night shift work, hazard, hormone receptor, menopausal status

1 Introduction

According to the latest study [1], breast cancer (BC) has surpassed lung cancer to become the most commonly occurring cancer in women and the leading cause of cancer death in female patients worldwide [2,3]. Among women, BC accounts for 1/4th among cancer cases and for 1 in 6 cancer deaths [1]. BC occurrence is widely believed to be influenced by both genetics (such as mutations in BRCA) [4,5] and risk factors in the environment [6–8]. Therefore, researchers are trying to come up with better prevention strategies for women by adjusting the exposure of BC factors [9,10]. Among all those risk factors, diet and lifestyle are considered to be relatively feasible to be adjusted [11,12]. For example, being sedentary [13], obese [14], smoking [15], eating high-fat and high-sugar foods [16,17] may cause the occurrence of BC.

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Long-term night shift work has also been identified as one of the potential risk factors for BC [18,19]. Several occupations are often faced with shifting timetables due to their nature. Some occupations require night shift workers to ensure the 24 h service, such as telecommunications broadcast workers [20], health care workers [21], aviation personnel [22], 24 h on-site service personnel [23], etc. Others need to provide security and maintain order, such as cemetery workers [24] and security personnel [25]. But night shift work is not in accordance with the human circadian rhythm [26]. The circadian rhythm disturbance resulting from the light at night [27] and shift working timetable [28] further leads to undesirable fluctuations in hormone secretion [29], thereby affecting human function [30]. In 2007, “shift work involving circadian disruption” was classified by the International Agency for Research on Cancer (IARC) as a probable cause for female BC (IARC Group 2A) based on sufficient animal [31] and limited epidemiological evidence [32]. In addition to this, the potential consequences of night shift work, including night eating [33], inverted sleep patterns [34], psychological depression [35], and so forth may also induce BC (occurrence).

Although shreds of evidence have shown that night shift work increases the risk of BC, studies in the past 30 years failed to investigate the clear association between night shift work and BC. Also, studies that have set up the length, frequency, and arrangement parameters of night shifts have shown high inconsistency when it comes to the results. In terms of observational research, a study by Lie et al. [36] demonstrated a significantly increased risk for nurses who worked >5 years with >6 consecutive night shifts. However, another study by Sweeney et al. [37] showed that though short-term nocturnal work and night shift work were associated with increased risk of developing BC, the 5-year night time work experience was not associated with a greater possibility of developing BC. Researchers have also reached inconsistent conclusions in many other meta-analyses [38,39]. The purpose of this study is to explore the relationship between night shift work and BC risk through systematic review and meta-analysis of current observational studies.

2 Materials and methods

2.1 Literature search

In the electronic databases of PubMed, Web of Science, the Cochrane Library, and EBSCO, a comprehensive literature search strategy was performed by retrieving the keywords “breast cancer” and “night-shift work” until June 2021. The complete formula used for retrieval was as follows: (“breast cancer” OR “breast neoplasms” OR “BC”) AND (“circadian disruption” OR “shift work” OR “night work” OR “night” OR “shift” OR “night-shift work” OR “rotating-shift work”). The references of included works of literature were manually reviewed to avoid omitting any potential studies. The population, intervention/exposure, comparison, outcome, and setting (PICOS) criteria were used to aid in the design of the study. This meta-analysis was conducted following the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [40]. This meta-analysis’s Prospero registration number was CRD42021270128.

2.2 Eligibility criteria and study selection

Specific eligible criteria were formulated as follows: inclusion criteria: (1) The study type falls into the category of observational studies. (2) The main exposure of study was night/shift work, and the outcome was BC risk. (3) The study has available data including hazard ratio (HR) and corresponding 95% confidence interval (CI). (4) The study was published in English. Exclusion criteria: (1) the study had no non-night/shift workers control group. (2) Patients with a previous history of concomitant BC. (3) The study was published in duplicate. (4) The study had no available full text.

Two authors (Jiaze Hong and Yujing He) independently applied a search strategy to select studies from the database and independently reviewed the titles and abstracts of these articles to judge whether they met the inclusion criteria. When in doubt, the full text will be searched for further selection. When necessary, authors are contacted for more information about their research. In case of disagreement, it was discussed with an independent third reviewer (Rongrong Fu). When consensus could not be reached, the study was excluded.

2.3 Data extraction

All data were extracted using mutually agreed data collection forms. In order to ensure the objectivity and accuracy of the entered data, two investigators (Yuexiu Si and Binbin Xu) independently extracted data from each study. Disagreements were resolved by consensus by
the two investigators or consultation with the third author (Jiaxuan Xu). Information, as follows, was extracted: the author’s name, year of publication, study type, country where the study was performed, age, follow-up time, number of participants, number of BC cases, variables adjusted in the statistical analyses, and outcomes (HR and 95% CI).

**2.4 Evaluation of quality of the studies**

The quality of each included study was evaluated and scored by using the Newcastle-Ottawa Quality Assessment Scale (NOS) checklist, a tool used for quality assessment of non-randomized studies. NOS checklist is classified into three aspects: selection, comparability, and outcome. The maximum score of this checklist is nine, and scores between six and nine were identified to be with higher study quality.

**2.5 Objectives and endpoints**

The primary aim of this study is to evaluate the relationship between night shift work and BC incidence. The secondary objective was to explore the relationship between the incidence of BC and the night shift subgroup, including length of work, frequency of work, cumulative times, age at which night work was initiated, and menopausal status. The adjusted outcomes were uniformly adopted for the processing of relevant data from the included articles.

**2.6 Statistical analysis**

The Stata software version 12 (Stata Corp, College Station, Texas, USA) was used to analyze the data. The CI of HR was set up at 95% to examine the relationship between night shift work and BC risk. To increase the credibility of the results, a random effect model was uniformly adopted in this study. Heterogeneity across included studies was tested by Q statistic and \( I^2 \) statistic to quantitatively evaluate the inconsistency. As for the statistic results, a value of \( p < 0.10 \) and \( I^2 > 50\% \) would be considered to be representative of statistically significant heterogeneity. Sensitivity analysis and publication bias tests were performed to evaluate the stability and reliability of the results when more than ten studies were included. Publication bias was evaluated by the Begg’s rank correlation test and Egger’s linear regression test. \( P \)-values less than 0.05 were considered to be statistically significant.

**Ethics approval and consent to participate:** Not applicable (this article was provided based on researching in global databases).

**3 Results**

**3.1 Literature search**

Through preliminary search in PubMed, EBSCO, Web of Science, and Cochrane Library databases, a total of 58,425 relevant articles were determined according to the search formula described in Section 2. No other record was identified from other sources. A total of 15,110 duplicate articles were deleted. 12,343 articles were excluded due to the title or abstract. The remaining 972 articles were reviewed through full-text reading. Among them, 939 articles were eliminated resulting from the following reasons: no non-night/shift workers were used as control \( (n = 817) \); duplicate publication \( (n = 79) \); no data available for extraction \( (n = 36) \); and non-English language \( (n = 7) \). Eventually, 33 articles \( [20–22,24,26,36,37,41–66] \) consisting of 4,331,782 participants were selected for this meta-analysis. The references of included studies were not included after review. The detailed search and study selection process is shown in Figure 1.

**3.2 Study characteristics**

Of the 33 included studies, 10 were cohort studies (4,076,375 participants and 50,686 BC cases), 22 were case-control studies (254,441 participants and 21,807 BC cases), and 1 was a cross-sectional study (966 participants and 56 BC cases). All participants were female. Among the selected studies, 18 studies were conducted in Europe, 7 in North America, 6 in Asia, and 2 in Australia. All studies were published between 1996 and 2021, with follow-up periods ranging from 4.9 to 30 years. Regarding age at recruitment, five studies did not set an upper age limit, and one study did not set a lower age limit. Sixteen studies defined the night shift work. Most studies did not put special requirements forward when it comes to the included participants. There were five studies for the nurse group, one study each in airline compartment attendants, textile workers, telecommunications broadcast workers, military, and electromagnetic field working
populations. In addition, the adjustment of potential confounding factors varied in different studies. Common adjustment parameters in the selected studies included age, body mass index (BMI), family history of BC, hormone replacement therapy (HRT), reproductive factors, total energy intake, smoking, alcohol consumption, and physical activity. In order to collect data and evaluate relevant exposure factors, 19 studies required a questionnaire, 9 studies chose interviews, and 5 studies combined both. The characteristics of the included studies are shown in Table 1 and Table S1.

### 3.3 Total night shift work

Twenty-five studies (568,838 participants) recorded data about BC risk of total night shift work on the female population. Among those, 18 were case-control studies (170,271 participants and 19,212 BC cases), 6 were cohort studies (397,601 participants and 7,769 BC cases), and 1 was a cross-sectional study (966 participants and 56 BC cases). The results showed that night shift work significantly increased the incidence of BC in women compared to those who never or rarely experienced night shifts \((HR = 1.20, 95\% CI = 1.10–1.31, p < 0.001)\). The heterogeneity in the included studies was significant \((I^2 = 76.3\%)\). The detailed data is displayed in Figure 2.

### 3.4 The duration of night shift work

Twenty-three out of the selected 33 studies discovered the relationship between the length of night shift work and the incidence of BC. In this study, the length of night shift work...
Table 1: Characteristics of included observational studies in the meta-analysis

| Author, year | Country     | Age of recruitment (year) | Age of analysis (year) | Follow-up time (year) | No. of cases | No. of participants | Characteristics                                                                 |
|-------------|-------------|---------------------------|------------------------|-----------------------|--------------|---------------------|--------------------------------------------------------------------------------|
| Wegrzyń LR, 2017 | America   | 25–55                     | 54.3 ± 7.2             | 24                   | 9,541        | 193,075             | The nurses’ health studies I and the nurses’ health studies II                  |
| Davis S, 2001    | America    | 20–74                     | 59.8 ± 6.4             | 6                    | 813          | 1,606               | NA                                                                              |
| Wang P, 2015    | China      | 22–85                     | 47.6 ± 11.1            | 5                    | 712          | 1,454               | NA                                                                              |
| Yang W, 2019     | China      | 18–74                     | 60.5 ± 8.7             | NA                   | 401          | 802                 | The Ji Jiang breast cancer study                                               |
| Åkerstedt T, 2015 | Sweden   | 41–60                     | 51.8 ± 4.7             | 13                   | 463          | 13,656              | The screening across the lifespan twin study                                    |
| Knutsson A, 2013 | Sweden     | 19–70                     | 38.9 ± 10.4            | 16.1                 | 94           | 4,036               | The WOLF (work, lipids, and fibrinogen) occupational cohort study               |
| Szkiela M, 2021  | Poland     | ≥35                       | 57.6 ± 3.9             | 12                   | 494          | 1,009               | NA                                                                              |
| Lie JA, 2011     | Norway     | 35–74                     | 54.4 ± 7.7             | 17                   | 699          | 1,594               | The Norwegian cohort of nurses                                                 |
| Tynes T, 1996    | Norway     | ≥50                       | 53.2 ± 10.8            | 30                   | 225          | 77,583              | The telecom cohort; the fertility cohort; the female occupational-cancer cohort |
| Lie JA, 2006     | Norway     | 27–85                     | 58.3 ± 6.4             | NA                   | 537          | 2,680               | NA                                                                              |
| Gómez-Salgado J, 2021 | Spain      | 25–60                     | 41.2 ± 10.6            | NA                   | 56           | 966                 | NA                                                                              |
| Papantoniou K, 2016 | Spain    | 20–85                     | 58.5 ± 0.3             | NA                   | 1,708        | 3,486               | MCC-Spain study                                                                |
| Hansen J, 2012   | Denmark    | 25–75                     | NA                     | 267                  | 1,302        |                      | A cohort of 91,140 female members of the Danish nurses association              |
| Hansen J, 2001   | Denmark    | 30–54                     | NA                     | 7,035                | 138,301      |                      | NA                                                                              |
| Hansen J, 2012   | Denmark    | 16–66                     | NA                     | 161                  | 692          |                      | A cohort of 18,551 female military employees born during 1929–1968             |
|Menegaux F, 2013  | France     | 25–75                     | 56.9 ± 3.1             | NA                   | 1,232        | 2,549               | The cell classification and in-vitro lifecycle evaluation study                 |
| Rabstejn S, 2013  | Germany    | 26–74                     | 56.2 ± 8.6             | NA                   | 857          | 1,749               | The gene environment interaction and breast cancer study                        |
| Grundy A, 2013   | Canada     | 20–80                     | 57.3 ± 10.3            | NA                   | 1,134        | 2,313               | NA                                                                              |
| Datta K, 2014    | India      | 30–65                     | 55.6 ± 2.6             | NA                   | 50           | 150                 | NA                                                                              |
| Fritschi L, 2013 | Australia  | 18–80                     | NA                     | 1,205                | 2,994        |                      | The Breast Cancer Employment and Environment Study                              |
| Kojo K, 2005     | Finland    | 38–81                     | 49.6 ± 9.4             | NA                   | 45           | 1098                | NA                                                                              |
| Bustamante-Montes LP, 2019 | Mexico | 25–65                     | 49.8 ± 11.3            | 5                    | 101          | 202                 | NA                                                                              |
| Pronk A, 2010    | China      | 40–70                     | 52.5 ± 9.1             | 9                    | 717          | 73,049              | The Shanghai women’s health study                                              |
| Li W, 2015       | China      | 30–80                     | 57.4 ± 10.5            | 11                   | 1,709        | 6,489               | A cohort of female textile workers in Shanghai                                   |
| Sweeney MR, 2020 | America    | 35–74                     | 48.3 ± 5.4             | 13                   | 3,191        | 48,451              | The sister study                                                               |
| O’Leary ES, 2006 | America    | ≤75                       | 59.0 ± 8.2             | NA                   | 576          | 1,161               | The electromagnetic Fields and breast cancer on Long Island study               |
| Jones ME, 2019   | Britain    | ≥16                       | 55.9 ± 5.6             | 15                   | 2,059        | 102,869             | The generations study cohort                                                   |
| Schwartzbaum J, 2007 | Sweden  | 15–80                     | 46.1 ± 3.5             | 18                   | 70           | 1,148,661           | NA                                                                              |
| Vistisen HT, 2017 | Denmark    | ≥18                       | NA                     | 4.9                  | 1,245        | 155,540             | NA                                                                              |
work is divided into three stages based on 10 and 30 years of night shift work. 20 studies (4,078,910 participants and 66,377 BC cases), 17 studies (3,936,466 participants and 57,411 BC cases), and 13 studies (3,813,835 participants and 51,642 BC cases) in the group of participants with a night shift work duration less than 10 years, 11 to 29 years, and more than 30 years have provided the incidence data of BC, respectively. The results showed that a duration of night shift work less than 10 years (HR = 1.09, 95% CI = 1.01–1.18, p = 0.032) (I² = 78.9%), between 11 and 29 years (HR = 1.12, 95% CI = 1.01–1.23, p = 0.034) (I² = 69.9%), and more than 30 years (HR = 1.18, 95% CI = 1.02–1.36, p = 0.024) (I² = 74.4%) will all increase the incidence of BC with a statistical significance. Also, year-round night work will increase the incidence of BC in women. The detailed data is shown in Table 2.

### 3.5 The frequency of night shift work

A total of 12 studies have provided data on elucidating the relationship between BC night shift work frequency, including 8 case-control studies and 4 cohort studies. This meta-analysis used the frequency of 5 night shifts per week as the boundary and divided the data into two groups: 1–5 times a week (2,525,009 participants and 41,758 BC cases) and more than 5 times a week (2,526,161 participants and 42,316 BC cases). Each group had 11 studies with extractable data. The results showed that when the night shift work frequency was 1–5 times a week, there was no significant effect on elevating the incidence of BC (HR = 1.08, 95% CI = 0.94–1.24, p = 0.308) (I² = 78.6%) (Figure 3a), while when the night shift work exceeded 5 times or more within a week, the incidence of BC would increase with a statistically significant difference (HR = 1.50, 95% CI = 1.02–2.20, p = 0.037) (I² = 95.0%) (Figure 3b). The results suggested that high-frequency night work is a risk factor to develop BC.

### 3.6 Cumulative times of night shift work

In terms of the cumulative number of night shifts, 7 studies were conducted on the female population. This meta-analysis grouped the data based on the cumulative number of night shifts of 500 and 1000. Through meta-analysis, the results showed that when the cumulative number of night work is less than 500 times (HR = 1.00, p = 0.976) (I² = 46.0%) or between 500–1,000 times (HR = 1.15, p = 0.404) (I² = 74.1%), there was no effect on the
incidence of BC. However, when the number hits 1000, the incidence rate of BC will increase, though the difference was not statistically significant (HR = 1.39, 95% CI = 0.99–1.95, p = 0.058) ($I^2 = 70.0\%$). The detailed data is given in Table 2.

### 3.7 Age at onset of night shift work

Five studies addressed the association of age at initiation of night shift work against the incidence of BC. Data were divided into “younger than 20 years group,” “20–29 years group,” “30–39 years group,” and “older than 40 years group.” The results showed that participants who started night work before age 20 (HR = 0.79, p = 0.220), started night work at age 20–29 (HR = 0.97, p = 0.728), started night work at age 30–39 (HR = 1.15, p = 0.138), or started night work at age 40 (HR = 0.85, p = 0.320) had no effect on BC incidence. The detailed data is given in Table 2.

### 3.8 Menopausal status

Six studies have data revealing the relationship between night shift work and the incidence of BC in people of

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**Figure 2:** Forest plot describing the association between night shift work and risk of BC.
Table 2: Effects of night/shift work on breast cancer incidence

| Subgroup analysis | No. of studies | No. of cases | HR | 95% CI | p     | Heterogeneity (I²) (%) |
|-------------------|----------------|--------------|----|--------|-------|------------------------|
| Night shift duration was 1–10 years | 20 | 66,377 | 1.09 | 1.01–1.18 | 0.032 | 78.9 |
| Night shift duration was 11–29 years | 17 | 57,411 | 1.12 | 1.01–1.23 | 0.034 | 69.9 |
| Night shift duration over 30 years | 14 | 51,642 | 1.14 | 1.02–1.26 | 0.024 | 46.0 |
| Cumulative night shifts exceeding 500 | 5 | 3,690 | 0.79 | 0.54–1.19 | 0.293 | 38.7 |
| Cumulative night shifts were 500–1,000 | 7 | 4,445 | 0.97 | 0.78–1.20 | 0.330 | 38.7 |
| Cumulative night shifts exceeding 1,000 | 6 | 4,389 | 1.39 | 1.02–1.89 | 0.058 | 70.8 |
| Age at initiation of night shift was less than 20 years old | 3 | 3,633 | 0.79 | 0.54–1.19 | 0.220 | 59.1 |
| Age at initiation of night shift was 20–29 years old | 5 | 5,410 | 0.97 | 0.78–1.20 | 0.728 | 0 |
| Age at initiation of night shift was 30–39 years old | 7 | 17,004 | 1.03 | 0.78–1.38 | 0.138 | 0 |
| Age at onset of night shift work was over 40 years old | 2 | 2,916 | 0.85 | 0.61–1.19 | 0.320 | 0 |

HR: hazard ratio; CI: confidence interval.

A total of 7 articles included aimed to discover the relationship between the night shift work and the types of BC. Seven studies (169,586 participants and 8,153 BC cases) classified the type of BC by estrogen receptor (ER), five studies (13,244 participants and 6,507 BC cases) classified according to progesterone receptor (PR), and five studies (16,624 participants and 996 BC cases) classified according to progesterone receptor (PR) and estrogen receptor (ER).

### 3.9 Menopausal status and duration of night shift work

A total of 8 studies explored the effect of different night shift durations on BC incidence in female populations with different menopausal statuses. The data of premenopausal and postmenopausal night shift work was stratified by 10 years of night shift work, of which, eight studies (345,472 participants and 17,004 BC cases) had extractable data for 1–9 years of night shift work and seven studies (341,436 participants and 16,910 BC cases) had extractable data for more than 10 years of night shift work. The results showed that for females who started night shift work before menopause, a 1–9 years of night shift work increased the incidence of BC (HR = 1.17, p = 0.016), but there was no fluctuation of BC incidence against a more than 10 years of night shift work experience (HR = 1.13, p = 0.170). The result was also true for females who started night shift work after menopause, with no influence by 1–9-year experience (HR = 0.96, p = 0.426) but an increase due to a 10-year experience (HR = 1.19, p = 0.026). The detailed data is presented in Table 2.

### 3.10 Different types of BC

A total of 7 articles included aimed to discover the relationship between the night shift work and the types of BC. Seven studies (169,586 participants and 8,153 BC cases) classified the type of BC by estrogen receptor (ER), five studies (13,244 participants and 6,507 BC cases) classified according to progesterone receptor (PR), and five studies (16,624 participants and 996 BC cases) classified according to progesterone receptor (PR) and estrogen receptor (ER).
(166,471 participants and 6,618 BC cases) classified according to human epidermal growth factor receptor 2 (HER2). The results of this meta-analysis showed that night shift work had a statistically significant effect on inducing receptor-positive BC, including ER+ BC (HR = 1.35, 95% CI = 1.19–1.53, \( p < 0.001 \)) \( (I^2 = 0\%) \) (Figure 5a), PR+ BC (HR = 1.30, 95% CI = 1.09–1.54, \( p = 0.003 \)) \( (I^2 = 33.8\%) \) (Figure 5b), and HER2+ BC (HR = 1.42, 95% CI = 1.17–1.72, \( p < 0.001 \)) \( (I^2 = 0\%) \) (Figure 5c). It would increase the incidence of receptor-positive BC in the female population. Whereas for HER2−BC (HR = 1.10, \( p = 0.515 \)) \( (I^2 = 79.9\%) \) (Figure 6a) or ER−/PR− BC (HR = 0.98, \( p = 0.827 \)) \( (I^2 = 0\%) \) (Figure 6b), night shift work was not an observable risk factor.

Figure 3: Forest plot describing the association between night shift work frequency and risk of BC. (a) 1–5 times per week. (b) More than 5 times a week.
3.11 Bias risk assessment

The NOS checklist was adopted in this meta-study in order to evaluate the quality of the included observational studies objectively. According to the results of the quality evaluation conducted by the investigators, 9 studies out of 33 were rated 9 points, 16 studies were rated 8 points, 6 studies were rated 7 points, and 2 studies were rated 6 points. All included studies were of high quality based on methodology. The Risk of bias assessments are documented in Table S2.

3.12 Publication bias and sensitivity analysis

For the subgroup with more than 10 included articles, sensitivity analysis and publication bias test were performed. Publication bias was evaluated by the Begg’s rank correlation and Egger’s linear regression test. In this meta-analysis, Begg’s rank correlation and Egger’s linear regression test indicated no publication bias among included articles regarding the HR ($p > 0.05$). Sensitivity analysis was applied to assess whether the individual

Figure 4: Forest plot describing the association between menopausal status at start of night shift work and risk of BC. (a) Night shift work started before menopause. (b) Night shift work started after menopause.
Figure 5: Forest plot depicting the association between night shift work and risk of receptor positive BC. (a) ER+ BC. (b) ER+ BC. (c) HER2+ BC.
study affected the overall results or not. The results illustrated that individual studies had little influence on the final results, and the analysis was relatively stable and credible (Figure S1).

4 Discussion

According to data analysis, we found that night shift work is a risk factor for BC. To be more detailed, night shift work can increase the incidence of BC in the female population, especially receptor-positive BCs, including ER+ BC, PR+ BC, and HER2+ BC, but no effect on HER2− and ER−/PR− BC. The risk of BC was positively correlated with night shift working duration, frequency, and cumulative times. There was no relationship between the age at initiation of night shift work and BC risk. Continuous night shift work for 1–10 years, 11–29 years, and more than 30 years increased the incidence of BC. Working more than 5 night shifts per week, and the cumulative number of night shifts exceeding 1,000 will increase the risk of BC, but the latter has not yet reached a statistically significant difference. For women who started night work before menopause, night work (especially 1–9 years) will increase the incidence of BC, but there will be no effect on those who work more than 10 years. For women who start night shift work after menopause, BC incidence will not be affected by night shift work until there is more than 10-year (night shift work) experience.

The mechanism of how night shift work can induce BC is still not thoroughly elucidated. The mainstream
among the dominant hypothesis is that circadian rhythm disturbances were caused by night shift work [67,68]. The mechanism by which circadian rhythm disorders may induce and/or promote the growth of malignant tumors is believed to be complex and multi-factorial [69]. Reduction in melatonin-dominated hormone secretion [70,71], which is resulted from the disrupted circadian rhythms, is considered as the most likely mechanism [72,73]. The multi-level changes in the endocrine system caused by circadian rhythm disturbance led to the possibility of carcinogenic of female endocrine-responsive breasts [74,75]. The abnormal fluctuation in endogenous hormone secretion due to circadian rhythm disturbance is a carcinogenic signal to the breast cells in female since they are sensitive to hormonal changes. The reduction in melatonin secretion may also be a trigger on the occurrence, promotion, and progression of tumor [76,77]. Several studies on night shift workgroups have shown that night shift work significantly reduces melatonin levels in plasma and delays the peak time of melatonin production [78,79]. The changes in level and time of melatonin production are carcinogenic. Moreover, related experiments have shown that melatonin can inhibit the development of different types of cancer in both in vitro and in vivo [80], and synergistically enhance the pharmacological effects of other anti-cancer drugs [81–83]. It is a chemical substance that can potentially be used as an adjuvant in chemotherapy in cancer treatment [84,85]. Several clinical studies have shown that although melatonin alone does not have the function of tumor regression, the accompanying prescription of melatonin can improve the efficacy of chemotherapy and radiotherapy with less unfavorable side effects [86–91].

When it comes to the cellular level, melatonin can protect cells from DNA damage caused by carcinogens. This is achieved by promoting DNA repair through activating related antioxidant pathways [62,92]. Night shift work-related circadian rhythm disruption reduces the secretion of melatonin, thus weakening the ability to repair DNA, leading to more susceptible cells being vulnerable to be affected by external carcinogens [93,94]. As for molecular level, melatonin can resynchronize the rhythm pattern of gene expression, correct the defects of various circadian genes responsible for cancer development in the expression pattern [95,96], and inhibit tumor signal transduction as well as the metabolic activity of cancer cells [97,98]. The disruption of melatonin signaling caused by night shifts upregulates tumor metabolism and stimulates its growth [99,100].

On the overall level, the reduction in melatonin production is upregulative to the gonadal axis [101,102]. As a response modifier of estrogen and progesterone, especially estradiol, melatonin exerts its anti-estrogen effect by interacting with ER-α [103–105] and inhibits the BC cell proliferation induced by estradiol [106–108]. At the same time, melatonin can downregulate the synthesis of protein growth factors and expression of proto-oncogenes stimulated by ER [109,110] and HER2, hence inhibiting the development of related BC [110–112]. Experimental evidence shows that inhibition of melatonin synthesis enhances the proliferation of ER-positive cell lines and promotes BC in HER-2 transgenic mice [113,114]. According to previous studies, long-term exposure to estrogen or increased cell response to estrogen in female is a noticeable risk factor for BC [114,115]. This may explain why night shift work lifts the risk of receptor-positive BC without any effect on HER2– and ER-/PR– BC. Besides, according to the study of Pham et al., night work has no effect on triple-negative BC [59]. In addition, premenopausal women, who depend more on endogenous estrogen secretion compared with postmenopausal women [18,116] normally have a rapid rate of gonadal axis upregulation in night shift work situations with the aid of active gonadal function, resulting in a high circulating level of estrogen in the body [117]. As mentioned, the overall effects of reduced melatonin on BC may partially explain that night-time work induces BC in women who started night shift work before menopause, whereas it has no effect on women who started night shift work after menopause.

The second supporting mechanism of increased risk of developing BC is that numerous hours of continuous night shift work are related to telomerase shortening [118]. Normal circadian rhythm can help maintain the length of telomerase thus adjusting its activity. Under normal circumstances, telomerase activity is influenced by the circadian rhythm, maintaining the length under the responsibility of telomerase [119,120]. Under the circumstances of night shift work, the circadian rhythm and sleep pattern are disrupted, inducing more error generated in the core circadian rhythm genes which regulate the telomere length and rhythm of activity, and eventually lead to telomere instability and DNA repair disorders [121,122]. Genome instability caused by telomere shortening is widely known as a mechanism of tumor development [118]. Moreover, long-term night work prevents the human body from getting enough rest time. In addition to that, continuous high-frequency night work may also represent a higher risk of human function disruption, making it difficult for the human body to quickly adjust itself into sleep mode and modulate the circadian rhythm [69]. This can explain why high frequency (more
than five times a week), long time (perennial), and multiple (over 1,000 times) night shifts increase the incidence of BC.

Recently, a relatively new hypothesis states that the suppression of immune surveillance caused by sleep deprivation at night, obesity induced by leptin secretion disorder, and changes in intestinal microbiota are also associated with the increased risk of BC. First of all, sleep deprivation changes the function of the immune system [72]. In the usual circadian sleep-wake mode, the balance between the Th1 cytokines (e.g., IL-2, IL-12, and interferon γ) which dominate during the day is shifted to the Th2 cytokines (e.g., IL4 and IL-10) which normally dominate during sleep at night [123,124]. This alteration reduces immune surveillance, silences the cellular immune response, and induces abnormal cell division, including tumor cells which may lead to malignant tumor [125,126]. Second, night shift work evokes a decrease in leptin level at night [127,128] as well as an imbalance in energy metabolism [70,129], resulting in night shift workers being more likely to be obese [14,130] and develop the metabolic syndrome [131,132]. Compared with other cancers, BC is more closely related to obesity, and obesity can increase the risk of BC through different mechanisms [133,134]. In addition, the imbalance of microbiota in the composition of the intestinal bacterial population (ecological dysbiosis) can change the level of estrogen in plasma [135,136]. On the one hand, this change is mainly caused by dysregulation of estradiol type bacteria, which have β-glucuronidase activity and favors estrogen in the deconjugated state, increasing the number of free estrogens in vascular circulation, which may potentially lead to BC [137–139]. On the other hand, it has been shown that these changes in the gut microbiota stimulate the kynurenine pathway, keeping tryptophan away from the melatonin pathway, reducing vascular circulating melatonin level, thereby increasing the risk of BC in women [138,139].

According to the above new views, we believe that for the women who start night shift work after menopause, 1–9 years of night shift work is too short to result in BC as a carcinogenic factor. When it comes to more than 10 years, the exposure to this carcinogenic factor has accumulated to a certain stage, making the risk of BC significantly greater. First of all, ovarian function declines sharply in women after menopause, together with the great reduction in estrogen secretion, while the number of ERs generally increase with age [140], making cells more sensitive to estrogen, which is an important risk factor for BC. Second, postmenopausal women’s autonomic nervous function will be disturbed, which can lead to abnormal metabolic activity in cells/organs [141]. With long-term night shift work, the metabolic rate will be significantly slower, and obesity is prone to induce BC [142,143]. Finally, postmenopausal females are prone to alteration of the gut microbiota. With long-term night work, the human body will aggravate imbalance by reducing the diversity of the microbiome and increasing the ratio of Firmicutes to Bacteroidetes [144–146]. These will lead to changes in estrogen, resulting in increased systemic estrogen level [147], combined with the increase in the number of postmenopausal ERs described in the first reason, which increases the risk of BC [37].

For women who started night shift work before menopause, we believe that the following three points may explain why 1–9 working years increase the risk of BC while there is no effect when it comes to more than 10 years. First of all, studies have shown that women under the age of 45 who are on night shifts from 11–20 years will increase the risk of early menopause by 25% [148]. The disturbance of circadian rhythm can affect ovulation and disrupt the regular menstrual cycle, which will induce ovarian failure and accelerate ovarian circulation. The estrogen in the vascular circulation is drastically reduced, which reduces the risk of exposure [26]. Second, as women age, their sleep patterns gradually turn to morning (wake up and fall asleep earlier), and the total length of sleep becomes shorter [149,150]. Studies have shown that longer sleep time (more than the recommended 7–8 h) increases the risk of BC [64] and people who sleep in the morning chronotype have a lower risk of BC than those who sleep in the evening chronotype [26,151]. Therefore, women’s sleep pattern changes with age and the reduction in duration reduces the risk factors for BC. Last but not least, women who started night shift work before menopause are more adapted to the night shift pattern after long night shift work, which means that their metabolism and the ability to regulate intestinal microbes are more in line with the new biological rhythm of night work or shift work in order to quickly adjust the break and circadian rhythm in sleep mode. In addition, we do not rule out the possibility that “some premenopausal women who work on shifts or short-term night work may switch to the daytime schedule earlier due to difficulty in adapting to the rotation or night time schedule,” thus making the effect on BC paradoxically insignificant after 10 years of night shift work in premenopausal women.

The study accomplished by Wang et al. [152] also performed a subgroup analysis based on discovering the relationship between night shift work frequency with BC. They found that each additional 500 times of night shift work would increase BC development by 13% (RR = 1.13, 95%
CI = 1.07–1.21), which is consistent with the results of our study. In addition, 5 of the 10 studies included in this meta-analysis were conducted in nurses whose night shift frequency and duration were more regular, making it easier for them to draw dose-response conclusions (that is, each additional night shift will increase certain BC risks). Dun et al.’s study [153] failed to find any relationship between night work and BC. (OR = 1.00, 95% CI = 0.98–1.03). The possible reason for this inconsistency is that some articles have analyzed the effects of night light and/or sleep interruption on BC in their meta-analysis, resulting in interference in the role of night shift work in BC and making research results less reliable.

Though this meta-analysis has reached a comprehensive and objective conclusion, there are still some potential limitations that need to be considered. First, all risk estimations included in the study used random effect models, but the design of methods, study population, sample size, risk assessment, and related confounding factor adjustments vary between studies, which may reduce the credibility of the conclusions. Second, most studies used questionnaires to assess night shift work, and there were also a few studies that employed interviews or questionnaires combined with interviews, making it inevitable that assessment bias or recall bias will arise during the evaluation of night shift work, especially in case-control studies nested in cohorts, which may have potentially biased our findings. Third, attention needs to be paid to the differences between the definition of night shift work in the included studies. There may be heterogeneity among the definitions based on working hours, working habits, and shift system among the observed population. Finally, not all trials have relevant subgroup data, such as BC type subgroup data, menopausal status subgroup data, and so on.

Despite these limitations, this meta-analysis has its own advantages. First, this research includes a great number of observational studies with more than 4 million participants in Asia, Europe, America, and Australia. The large observation population lifts the reliability and authenticity of the conclusions of this study. Second, the study chose to adjust the relevant data of the largest number of potential confounding factors for statistical analysis to improve the accuracy of the conclusions. Finally, the study grouped abstract data (according to BC type, menopausal status or night work frequency, night work duration, the accumulated number of night work, etc.), and conducted subgroup analysis to comprehensively screen for the possibility of the effect of night shift work on different populations and on different BC types. Overall, this meta-analysis has reached some meaningful conclusions, which may provide new recommendations for the prevention of BC in the female population and for employers to formulate a more reasonable night shift system.

5 Conclusion

This meta-analysis found that night shift work increases the risk of BC in women, especially receptor-positive BC subtypes, including ER+ BC, PR+ BC, HER2+ BC, and has no effect on HER2− BC and ER−/PR− BC. The risk of BC was positively correlated with night shift working duration, frequency, and cumulative total times. For women who start night work before menopause, night work will increase the incidence of BC, but for women who start night work after menopause, night work has no effect on BC. However, based on the consideration of related limitations, a large-scale prospective cohort study is still needed to further confirm the research conclusions.

Abbreviations

| Abbreviation | Definition                        |
|--------------|----------------------------------|
| BC           | breast cancer                    |
| BMI          | body mass index                  |
| CI           | confidence interval              |
| ER           | estrogen receptor                |
| HER2         | human epidermal growth factor receptor 2 |
| HR           | hazard ratio                     |
| HRT          | hormone replacement therapy      |
| IARC         | international agency for research on cancer |
| MOOSE        | the meta-analysis of observational studies in epidemiology |
| NOS          | the Newcastle-Ottawa quality assessment scale checklist |
| PICOS        | the population, intervention, comparison, outcome and setting criteria |
| PR           | progesterone receptor            |

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extracted useful information from the articles above. Binbin Xu and Jiaxuan Xu used statistical software for analysis. Jiaze Hong and Yujing He drafted the meta-analysis. Xiangyuan Li polished this article. All authors had read and approved the manuscript and ensured that this was the case.

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References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
[2] Akram M, Iqbal M, Daniyal M, Khan AU. Awareness and current knowledge of breast cancer. Biol Res. 2017;50(1):33.
[3] Geetharamani R, Sivagami G. Iterative principal component analysis method for improvised classification of breast cancer disease using blood sample analysis. Med Biol Eng Comput. 2021;59(10):1973–89.
[4] Kwong A, Shin YY, Ho IC, Kang E, Nakamura S, Teo SH, et al. Comprehensive spectrum of BRCA1 and BRCA2 deleterious mutations in breast cancer in Asian countries. J Med Genet. 2016;53(1):15–23.
[5] Lee A, Moon BI, Kim TH. BRCA1/BRCA2 pathogenic variant breast cancer: treatment and prevention strategies. Ann Lab Med. 2020;40(2):114–21.
[6] Park SY, Kolonel LN, Lim U, White KK, Henderson BE, Wilkens LR. Alcohol consumption and breast cancer risk among women from five ethnic groups with light to moderate intakes: the multiethnic cohort study. Int J Cancer. 2014;134(6):1504–10.
[7] Rieder V, Salama M, Glockner L, Muhr D, Berger A, Tea MK, et al. Effect of lifestyle and reproductive factors on the onset of breast cancer in female BRCA 1 and 2 mutation carriers. Mol Genet Genomic Med. 2016;4(2):172–7.
[8] Zbuk K, Anand SS. Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. J Epidemiol Community Health. 2012;66(1):1–7.
[9] Mourouti N, Kontogianni MD, Papavagelis C, Panagiotakos DB. Diet and breast cancer: a systematic review. Int J Food Sci Nutr. 2015;66(1):1–42.
[10] Youn HJ, Han W. A review of the epidemiology of breast cancer in Asia: Focus on risk factors. Asian Pac J Cancer Prev. 2020;21(4):867–80.
[11] Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, et al. Breast cancer: Biology, biomarkers, and treatments. Int Immunopharmacol. 2020;84:106535.
[12] Li Y, Li S, Meng X, Gan RY, Zhang JJ, Li HB. Dietary Natural Products for Prevention and Treatment of Breast Cancer. Nutrients. 2017;9(7):728.
[13] Godinho-Mota JCM, Goncalves LV, Mota JF, Soares LR, Schincaglia RM, Martins KA, et al. Sedentary behavior and alcohol consumption increase breast cancer risk regardless of menopausal status: A case-control study. Nutrients. 2019;11(8):1871.
[14] Pierobon M, Frankenfeld CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. Breast Cancer Res Treat. 2013;137(1):307–14.
[15] Duan W, Li S, Meng X, Sun Y, Jia C. Smoking and survival of breast cancer patients: A meta-analysis of cohort studies. Breast. 2017;33:117–24.
[16] Chlebowski RT, Aragaki AK, Anderson GL, Thomson CA, Manson JE, Simon MS, et al. Low-fat dietary pattern and breast cancer mortality in the women’s health initiative randomized controlled trial. J Clin Oncol. 2017;35(25):2919–26.
[17] Goncalves RM, Delgobo M, Agnes JP, das Neves RN, Falchetto M, Casagrande T, et al. COX-2 promotes mammary adipose tissue inflammation, local estrogen biosynthesis, and carcinogenesis in high-sugar/fat diet treated mice. Cancer Lett. 2021;502:44–57.
[18] Cordina-Duverger E, Koudou Y, Truong T, Arveux P, Kerbrat P, Menegaux F, et al. Night work and breast cancer risk defined by human epidermal growth factor receptor-2 (HER2) and hormone receptor status: A population-based case-control study in France. Chronobiol Int. 2016;33(6):783–7.
[19] Hadadi E, Taylor W, Li XM, Aslan Y, Villote M, Riviere J, et al. Chronic circadian disruption modulates breast cancer stemness and immune microenvironment to drive metastasis in mice. Nat Commun. 2020;11(1):3193.
[20] Tynes T, Hannevik M, Andersen A, Vistnes AI, Haldorsen T. Incidence of breast cancer in Norwegian female radio and telegraph operators. Cancer Causes Control. 1996;7(2):197–204.
[21] Lie JA, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. Cancer Causes Control. 2006;17(1):39–44.
[22] Kojo K, Pukkala E, Auvinen A. Breast cancer risk among Finnish cabin attendants: a nested case-control study. Occup Environ Med. 2005;62(7):488–93.
[23] Patterson PD, Mountz KA, Budd CT, Bubb JL, Hsin AU, Weaver MD, et al. Impact of shift work on blood pressure among emergency medical services clinicians and related shift workers: A systematic review and meta-analysis. Sleep Health. 2020;6(3):387–98.
[24] Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. J Natl Cancer Inst. 2001;93(20):1557–62.
[25] Lim YC, Hoe VCW, Darus A, Bhoo-Pathy N. Association between night-shift work, sleep quality and health-related quality of life: a cross-sectional study among manufacturing workers in a middle-income setting. BMJ Open. 2020;10(9):e034455.
[26] Szkiela M, Kusidel E, Makowiec-Dabrowska T, Kaleta D. How the intensity of night shift work affects breast cancer risk. Int J Environ Res Public Health. 2021;18(9):4570.
[27] Stevens RG. Electric power use and breast cancer: a hypothesis. Am J Epidemiol. 1987;125(4):556–61.

[28] Fagundo-Rivera J, Gomez-Salgado J, Garcia-Iglesias JJ, Gomez-Salgado C, Camacho-Martín S, Ruiz-Frutos C. Relationship between night shifts and risk of breast cancer among nurses: a systematic review. Medicina (Kaunas). 2020;56(12):680.

[29] Wei W, Zhao W, Zhang Y. CBX4 provides an alternate mode of colon cancer development via potential influences on circadian rhythm and immune infiltration. Front Cell Dev Biol. 2021;9:669254.

[30] Cable J, Schernhammer E, Hanlon EC, Vetter C, Cedernaes J, Lie JA, Kjuus H, Zienolddiny S, Haugen A, Stevens RG, Samet JM, Lie JA, Lohrisch C, SenGupta SK, Datta K, Roy A, Nanda D, Das I, Guha S, Ghosh D, et al. Sleep and circadian rhythms: pillars of health and disease. Am J Epidemiol. 2011;173(3):313–21.

[31] Lauren S, Chen Y, Friel C, Chang BP, Shechter A. Free-living sleep, food intake, and physical activity in night and morning shift workers. J Am Coll Nutr. 2020;39(5):450–6.

[32] Papantoniou K, Castano-Vinyals G, Espinosa A, Turner MC, Martin-Sanchez V, Casabonne D, et al. Sleep duration and napping in relation to colorectal and gastric cancer in the MCC-Spain study. Sci Rep. 2021;11:11822.

[33] Yasin AI, Topcu A, Shbair AT, Isleyen ZS, Ozturk A, Besirgül M, et al. Anxiety levels of breast cancer patients in Turkey during the COVID-19 pandemic. Future Oncol. 2021;17(25):3373–81.

[34] Lie JA, Kjus H, Zienolddiny S, Haugen A, Stevens RG, Fagundo R, Ardanaz E, et al. Night work and breast cancer risk among Norwegian nurses: assessment by different exposure metrics. Am J Epidemiol. 2011;173(11):1272–9.

[35] Sweeney MR, Sandler DP, Niehoff NM, White AJ. Night work and working at night in relation to breast cancer incidence. Cancer Epidemiol Biomarkers Prev. 2020;29(3):687–9.

[36] Liu W, Zhou Z, Dong D, Sun L, Zhang G. Sex differences in the association between night work shift and the risk of cancers: a meta-analysis of 57 articles. Dis Markers. 2018;2018:792519.

[37] Manouchehr E, Taghipour A, Ghavami V, Ebadi A, Homaei F, Latifnejad Roudsari R. Night-shift work duration and breast cancer risk: an updated systematic review and meta-analysis. BMC Womens Health. 2021;21(1):89.

[38] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting, meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA. 2000;283(15):2008–12.

[39] Akerstedt T, Knutsson A, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. Night work and breast cancer in women: a Swedish cohort study. BMJ Open. 2015;5(4):e008127.

[40] Bustamante-Montes LP, Flores-Meza B, Hernandez-Valero MA, Cardenas-Lopez A, Dolores-Velazquez R, Borja-Bustamante P, et al. Night shift work and risk of breast cancer in women. Arch Med Res. 2019;50(6):393–9.

[41] Datta K, Roy A, Nanda D, Das I, Guha S, Ghosh D, et al. Association of breast cancer with sleep pattern: a pilot case control study in a regional cancer centre in South Asia. Asian Pac J Cancer Prev. 2014;15(20):8641–5.

[42] Fernandez RC, Peters S, Carey RN, Davies MJ, Fritschi L. Assessment of exposure to shiftwork mechanisms in the general population: the development of a new job-exposure matrix. Occup Environ Med. 2014;71(10):723–9.

[43] Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, et al. The association between different night shift work factors and breast cancer: a case-control study. Br J Cancer. 2013;109(9):2472–80.

[44] Gomez-Salgado J, Fagundo-Rivera J, Ortega-Moreno M, Allande-Cusso R, Ayuso-Murillo D, Ruiz-Frutos C. Night work and breast cancer risk in nurses: multifactorial risk analysis. Cancers (Basel). 2021;13:6.

[45] grundy A, richardson H, Burstyn I, Lohrisch C, SenGupta SK, Lai AS, et al. Increased risk of breast cancer associated with long-term shift work in Canada. Occup Environ Med. 2013;70(12):831–8.

[46] Hansen J. Increased breast cancer risk among women who work predominantly at night. Epidemiology. 2001;12(1):74–7.

[47] Hansen J, Lassen CF. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. Occup Environ Med. 2012;69(8):551–6.

[48] Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. Eur J Cancer. 2012;48(11):1722–9.

[49] Harris MA, MacLeod J, Kim J, Papaw M, Tjepkema M, Peters P, et al. Use of a Canadian Population-Based Surveillance Cohort to Test Relationships Between Shift Work and Breast, Ovarian, and Prostate Cancer. Ann Work Expo Health. 2020;64(4):387–401.

[50] Jones ME, Schoemaker MJ, McFadden EC, Wright LB, Johns LE, Swerdlow AJ. Night shift work and risk of breast cancer in women: the generations study cohort. Br J Cancer. 2019;121(2):172–9.

[51] Knutsson A, Alfredsson L, Karlsson B, Akerstedt T, Fransson EL, Westerholm P, et al. Breast cancer among shift workers: results of the WOLF longitudinal cohort study. Scand J Work Environ Health. 2013;39(2):170–7.

[52] Koppes LL, Geuskens GA, Pronk A, Vermeulen RC, de Vroome EM. Night work and breast cancer risk in a general population prospective cohort study in the Netherlands. Eur J Epidemiol. 2014;29(8):577–84.

[53] Li W, Ray RM, Thomas DB, Davis S, Yost M, Breslow N, et al. Shift work and breast cancer among women textile workers in Shanghai, China. Cancer Causes Control. 2015;26(1):143–50.

[54] Menegaux F, Truong T, Anger A, Cordina-Duverger E, Lamkarkach F, Arveux P, et al. Night work and breast cancer: a population-based case-control study in France (the CECLISE study). Int J Cancer. 2013;132(4):924–31.

[55] O’Leary ES, Schoenfeld ER, Stevens RG, Kabat GC, Henderson K, Grimson R, et al. Shift work, light at night, and breast cancer on Long Island, New York. Am J Epidemiol. 2006;164(4):358–66.

[56] Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Ardanaz E, et al. Breast cancer risk and night shift work in a case-control study in a Spanish population. Eur J Epidemiol. 2016;31(9):867–78.
[59] Pham TT, Hwang M, Lee ES, Kong SY, Jung SY, Lee S, et al. Night-shift work and risk of breast cancer in Korean women. Clin Epidemiol. 2019;11:743–51.

[60] Pronk A, Ji BT, Shu XO, Xue S, Yang G, Li HL, et al. Night-shift work and breast cancer risk in a cohort of Chinese women. Am J Epidemiol. 2010;171(9):953–9.

[61] Rabenstein S, Harth V, Pesch B, Pallapies D, Lotz A, Justenhoven C, et al. Night work and breast cancer estrogen receptor status-results from the German GENICA study. Scand J Work Env Health. 2013;39(5):448–55.

[62] Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. Scand J Work Env Health. 2007;33(5):336–43.

[63] Vistisen HT, Garde AH, Frydenberg M, Christiansen P, Hansen AM, Hansen J, et al. Short-term effects of night shift work on breast cancer risk: a cohort study of payroll data. Scand J Work Env Health. 2017;43(1):59–67.

[64] Wang P, Ren FM, Lin Y, Su FX, Jia WH, Su XF, et al. Night-shift work, sleep duration, daytime napping, and breast cancer risk. Sleep Med. 2015;16(4):462–8.

[65] Wegryn LR, Tamimi RM, Rosner BA, Brown SB, Stevens RG, Eliassen AH, et al. Rotating night-shift work and the risk of breast cancer in the nurses’ health studies. Am J Epidemiol. 2017;186(5):510–20.

[66] Yang W, Shi Y, Ke X, Sun H, Guo J, Wang X. Long-term sleep habits and the risk of breast cancer among Chinese women: a case-control study. Eur J Cancer Prev. 2019;28(4):323–9.

[67] Benca R, Duncan MJ, Frank E, McClung C, Nelson RJ, Vicent C. Biological rhythms, higher brain function, and behavior: Gaps, opportunities, and challenges. Brain Res Rev. 2009;62(1):57–70.

[68] Wood PA, Du-Quilton J, You S, Hrushesky WJ. Circadian clock coordinates cancer cell cycle progression, thyimidine synthase, and 5-fluorouracil therapeutic index. Mol Cancer Ther. 2006;5(8):2023–33.

[69] Costa G, Haus E, Stevens R. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. Scand J Work Env Health. 2010;36(2):163–79.

[70] Froy O. Metabolism and circadian rhythms–implications for obesity. Endocr Rev. 2010;31(1):1–24.

[71] Oster H, Damerow S, Hut RA, Eichele G. Transcriptional profiling in the adrenal gland reveals circadian regulation of hormone biosynthesis genes and nucleosome assembly genes. J Biol Rhythm. 2006;21(5):350–61.

[72] Hriscu M, Saulea G, Ostriceanu S, Baciuc I. Circadian phagocytic activity in rats under light–dark and constant light regimens. Rom J Physiol. 2002;39:40–17–26.

[73] Wulf K, Porcheret K, Cussans E, Foster RG. Sleep and circadian rhythm disturbances: multiple genes and multiple phenotypes. Curr Opin Genet Dev. 2009;19(3):237–46.

[74] Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. Endocrine. 2005;27(2):189–200.

[75] Lincoln DW 2nd, Hrushesky WJ, Wood PA. Circadian organization of thymidylate synthase activity in normal tissues: a possible basis for 5-fluorouracil chronotherapeutic advantage. Int J Cancer. 2000;88(3):479–85.

[76] Carrillo-Vico A, Reiter RJ, Lardone PJ, Herrera JL, Fernandez-Montesinos R, Guerrero JM, et al. The modulatory role of melatonin on immune responsiveness. Curr Opin Investig Drugs. 2006;7(5):423–31.

[77] Dubocovich ML, Markowska M. Functional MT1 and MT2 melatonin receptors in mammals. Endocrine. 2005;27(2):101–10.

[78] Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castano-Vinyals G, Basagana X, et al. Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes. Cancer Epidemiol Biomarkers Prev. 2014;23(7):1176–86.

[79] Razavi P, Devore EE, Bajaj A, Lockley SW, Figueiro MG, Ricchiuti V, et al. Shift Work, Chronotype, and Melatonin Rhythm in Nurses. Cancer Epidemiol Biomarkers Prev. 2019;28(7):1177–86.

[80] Alonso-Gonzalez C, Gonzalez A, Martinez-Campa C, Gomez-Arozamena J, Cos S. Melatonin sensitizes human breast cancer cells to ionizing radiation by downregulating proteins involved in double-strand DNA break repair. J Pineal Res. 2015;58(2):189–97.

[81] Alonso-Gonzalez C, Menendez-Menendez J, Gonzalez-Gonzalez A, Gonzalez A, Cos S, Martinez-Campa C. Melatonin enhances the apoptotic effects and modulates the changes in gene expression induced by docetaxel in MCF7 human breast cancer cells. Int J Oncol. 2018;52(2):560–70.

[82] Talib WH, Saleh S. Propionibacterium acnei augments anti-tumor, anti-angiogenesis and immunomodulatory effects of melatonin on breast cancer implanted in mice. PLoS One. 2015;10(4):e0124384.

[83] Wang J, Guo W, Chen W, Yu W, Tian Y, Fu L, et al. Melatonin potentiates the antiproliferative and pro-apoptotic effects of ursolic acid in colon cancer cells by modulating multiple signaling pathways. J Pineal Res. 2013;54(4):406–16.

[84] Bojkova B, Kubatka P, Qaradaki T, Zulli A, Kajo K. Melatonin may increase anticancer potential of pleiotropic drugs. Int J Mol Sci. 2018;19(12):3910.

[85] Odeh LH, Talib WH, Basheti IA. Synergistic effect of thymoquinone and melatonin against breast cancer implanted in mice. J Cancer Res Ther. 2018;14(Supplement):S324–S30.

[86] Farhood B, Goradel NH, Mortezaei K, Khanlarkhani N, Salehi E, Nashtaei MS, et al. Melatonin as an adjuvant in radiotherapy for radioprotection and radiosensitization. Clin Transl Oncol. 2019;21(3):268–79.

[87] Favero G, Moretti E, Bonomini F, Reiter RJ, Rodella LF, Rezzani R. Promising antineoplastic actions of melatonin. Front Pharmacol. 2018;9:1066.

[88] Kim C, Kim N, Joo H, Youm JB, Park WS, Cuong DV, et al. Modulation by melatonin of the cardiotoxicity and antitumor activities of adriamycin. J Cardiovasc Pharmacol. 2005;46(2):200–10.

[89] Liu D, Ma Z, Di S, Yang Y, Yang J, Xu L, et al. AMPK/PGC1alpha activation by melatonin attenuates acute doxorubicin cardiotoxicity via alleviating mitochondrial oxidative damage and apoptosis. Free Radic Biol Med. 2018;129:59–72.

[90] Martinez-Campa C, Menendez-Menendez J, Alonso-Gonzalez C, Gonzalez A, Alvarez-Garcia V, Cos S. What is known about melatonin, chemotherapy and altered gene expression in breast cancer. Oncol Lett. 2017;13(4):2003–14.
Oz E, Erbas D, Surucu HS, Duzgun E. Prevention of doxorubicin-induced cardiotoxicity by melatonin. Mol Cell Biochem. 2006;282(1-2):31–7.

Blask DE, Sauer LA, Dauchy RT. Melatonin as a chronobiologic/anticancer agent: cellular, biochemical, and molecular mechanisms of action and their implications for circadian-based cancer therapy. Curr Top Med Chem. 2002;2(2):113–32.

Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night: the neuroendocrine/circadian melatonin signal. Endocrine. 2005;27(2):179–88.

Su SC, Hsieh MJ, Yang WE, Chung WH, Reiter RJ, Yang SF. Cancer metastasis: Mechanisms of inhibition by melatonin. J Pineal Res. 2017;62(1).

Galijasevic S, Abdulhamid I, Abu-Soud HM. Melatonin is a potent inhibitor for myeloperoxidase. Biochemistry. 2008;47(8):2668–77.

Jung-Hynes B, Huang W, Reiter RJ, Ahmad N. Melatonin resynchronizes dysregulated circadian rhythm circuity in human prostate cancer cells. J Pineal Res. 2010;49(1):60–8.

Hill SM, Frasch T, Xiang S, Yuan L, Duplessis T, Mao L. Molecular mechanisms of melatonin anticancer effects. Integr Cancer Ther. 2009;8(4):337–46.

Wheatley-Price P, Asomaning K, Reid A, Zhai R, Su L, Zhou W, et al. Myeloperoxidase and superoxide dismutase polymorphisms are associated with an increased risk of developing pancreatic adenocarcinoma. Cancer. 2008;112(5):1037–42.

Blask DE, Dauchy RT, Brainard GC, Hanifin JP. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. Integr Cancer Ther. 2009;8(4):347–53.

Sliwinska T, Rozej W, Morawiec Bajda A, Morawiec Z, Reiter R, Blasiak J. Protective action of melatonin against oxidative DNA damage: chemical inactivation versus base-excision repair. Mutat Res. 2007;634(1-2):220–7.

Nagata C, Nagao Y, Yamamoto S, Shibuya C, Kashiki Y, Shimizu H. Light exposure at night, urinary 6-sulfatoxymelatonin, and serum estrogens and androgens in postmenopausal Japanese women. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1418–23.

Scherhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. Cancer Epidemiol Biomarkers Prev. 2004;13(6):936–43.

Baldwin WS, Barrett JC. Melatonin: receptor-mediated events that may affect breast and other steroid hormone-dependent cancers. Mol Carcinog. 1998;21(3):149–55.

Collins A, Yuan L, Kiefer TL, Cheng Q, Lai L, Hill SM. Overexpression of the MT1 melatonin receptor in MCF-7 human breast cancer cells inhibits mammary tumor formation in nude mice. Cancer Lett. 2003;189(1):49–57.

Ram PT, Dai J, Yuan L, Dong C, Kiefer TL, Lai L, et al. Involvement of the mt1 melatonin receptor in human breast cancer. Cancer Lett. 2002;179(2):141–50.

Blask DE, Hill SM. Effects of melatonin on cancer: studies on MCF-7 human breast cancer cells in culture. J Neural Transm Suppl. 1986;21:433–49.

Cos S, Fernandez R, Guezmés A, Sanchez-Barcelo EI. Influence of melatonin on invasive and metastatic properties of MCF-7 human breast cancer cells. Cancer Res. 1998;58(19):4383–90.

Leon-Blanco MM, Guerrero JM, Reiter RJ, Calvo JR, Pozo D. Melatonin inhibits telomerase activity in the MCF-7 tumor cell line both in vivo and in vitro. J Pineal Res. 2003;35(3):204–11.

Mediavilla MD, Guezméz A, Ramos S, Kohli L, Garijo F, Sanchez, et al. Effects of melatonin on mammary gland lesions in transgenic mice overexpressing N-ras proto-oncogene. J Pineal Res. 1997;22(2):86–94.

Molis TM, Spriggs LL, Jupiter Y, Hill SM. Melatonin modulation of estrogen-regulated proteins, growth factors, and proto-oncogenes in human breast cancer. J Pineal Res. 1995;18(2):93–103.

Baturin DA, Alimova IN, Anisimov VN, Popovich IG, Zabezhinsky MA, Provinciali M, et al. The effect of light regimen and melatonin on the development of spontaneous mammary tumors in HER-2/neu transgenic mice is related to a downregulation of HER-2/neu gene expression. Neuro Endocrinol Lett. 2001;22(6):441–7.

Cos S, Martínez-Campa C, Mediavilla MD, Sanchez-Barcelo EJ. Melatonin modulates aromatase activity in MCF-7 human breast cancer cells. J Pineal Res. 2005;38(2):136–42.

Anisimov VN, Alimova IN, Baturin DA, Popovich IG, Zabezhinsky MA, Manton KG, et al. The effect of melatonin treatment regimen on mammary adenocarcinoma development in HER-2/neu transgenic mice. Int J Cancer. 2003;103(3):300–5.

Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. JAMA. 2002;288(7):872–81.

Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879–86.

Daly AA, Rolph R, Cutress RI, Copson ER. A review of modifiable risk factors in young women for the prevention of breast cancer. Breast Cancer (Dove Med Press). 2021;13:241–57.

Pesch B, Harth V, Rabstein S, Baisch C, Schiessl J, Samuel ME, et al. A review of modifiable risk factors in young women for the prevention of breast cancer. Breast Cancer (Dove Med Press). 2021;13:241–57.

Samužin Endem J, Noto HO, Skare O, Petersen-Oleinik M, Reszka E, et al. Mechanisms of breast cancer risk in shift workers: association of telomere length and cancer: a meta-analysis. Scand J Work Environ Health. 2010;36(2):134–41.

Wentzensen IM, Mirabella L, Pfeiffer RM, Savage SA. The association of telomere length and cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2011;20(6):1238–50.

De Lange T. Telomere-related genome instability in cancer. Cold Spring Harb Symp Quant Biol. 2005;70:197–204.

Gomez DE, Armando RG, Farina HG, Menna PL, Cerrudo CS, Ghiringhelli PD, et al. Telomere structure...
and telomerase in health and disease (review). Int J Oncol. 2012;41(5):1561–9.

[123] Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol. 1997;158(9):4454–64.

[124] Mocellin S, Marincola FM, Young HA. Interleukin-10 and the immune response against cancer: a counterpoint. J Leukoc Biol. 2005;78(5):1043–51.

[125] Dimitrov S, Lange T, Tieken S, Fehm HL, Born J. Sleep associated regulation of T helper 1/T helper 2 cytokine balance in humans. Brain Behav Immun. 2004;18(4):341–8.

[126] Petrovsky N. Towards a unified model of neuroendocrine-immune interaction. Immunol Cell Biol. 2001;79(4):350–7.

[127] Spiegel K, Leproult R, L’Hermitte-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab. 2004;89(11):5762–71.

[128] Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141(11):846–50.

[129] Fleury G, Masis-Vargas A, Kalsbeek A. Metabolic implications of exposure to light at night: lessons from animal and human studies. Obes (Silver Spring). 2020;28(Suppl 1):S18–28.

[130] Picon-Ruiz M, Morata-Tarifa C, Valles-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA Cancer J Clin. 2017;67(5):378–97.

[131] Campbell PT, Newton CC, Petal AV, Jacobs EJ, Gapstur SM. Diabetes and cause-specific mortality in a prospective cohort of one million U.S. adults. Diabetes Care. 2012;35(9):1835–44.

[132] Gallagher EJ, LeRoith D. Obesity and Diabetes: The Increased Risk of Cancer and Cancer-Related Mortality. Physiol Rev. 2015;95(3):727–48.

[133] Goodwin PJ, Stambolic V. Impact of the obesity epidemic on cancer. Annu Rev Med. 2015;66:281–96.

[134] Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D, et al. Cancer incidence and mortality in relation to body mass index in the million women study: cohort study. BMJ. 2007;335(7630):1134.

[135] Laborda-llanes A, Sanchez-Alcoholado L, Boutiqr S, Plaza-Andrades I, Peralta-Linero J, Alba E, et al. A new paradigm in the relationship between melanin and breast cancer: gut microbiota identified as a potential regulatory agent. Cancers (Basel). 2021;13:13.

[136] Mei Q, Diao L, Xu JM, Liu XC, Jin J. A protective effect of melatonin on intestinal permeability is induced by diclofenac via regulation of mitochondrial function in mice. Acta Pharmacol Sin. 2011;32(4):495–502.

[137] Fernandez MF, Reina-Perez I, Astorga JM, Rodriguez-Carrillo A, Plaza-Diaz J, Fontana L. Breast cancer and its relationship with the microbiota. Int J Environ Res Public Health. 2018;15(8):1747.

[138] Rodriguez M, Woottla B, Anderson G. Multiple sclerosis, gut microbiota and permeability: role of tryptophan catabolites, depression and the driving down of local melatonin. Curr Pharm Des. 2016;22(40):6134–41.

[139] Voigt RM, Forsyth CB, Green SJ, Mutlu E, Engen P, Vitaterna MH, et al. Circadian disorganization alters intestinal microbiota. PLoS One. 2014;9(5):e97500.

[140] Santandrea G, Bellarosa C, Gibertoni D, Cucchi MC, Sanchez AM, Franceschini G, et al. Hormone receptor expression variations in normal breast tissue: preliminary results of a prospective observational study. J Pers Med. 2021;11(5):387.

[141] Becker SL, Manson JE. Menopause, the gut microbiome, and weight gain: correlation or causation? Menopause. 2020;28(3):327–31.

[142] Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer. 2007;121(4):856–62.

[143] Mayneris-Perxach J, Armoriaga-Rodriguez M, Luque-Cordoba D, Priego-Capote F, Perez-Brocal V, Moya A, et al. Gut microbiota steroid sexual dimorphism and its impact on gonadal steroids: influences of obesity and menopausal status. Microbiome. 2020;8(1):136.

[144] Baker JM, Al-Nakkash L, Herbst-Kralovez MM. Estrogen-gut microbiome axis: Physiological and clinical implications. Maturitas. 2017;103:45–53.

[145] Schreurs MPH, de Vos van Steenwijck PJ, Romano A, Dieleman S, Werner HMJ. How the gut microbiome links to menopause and obesity, with possible implications for endometrial cancer development. J Clin Med. 2021;10(13).

[146] Singer-Englar T, Barlow G, Mathur R. Obesity, diabetes, and the gut microbiome: an updated review. Expert Rev Gastroenterol Hepatol. 2019;13(1):3–15.

[147] Kwa M, Plotter CS, Blaser MJ, Adams S. The intestinal microbiome and estrogen receptor-positive female breast cancer. J Natl Cancer Inst. 2016;108(8):djw029.

[148] Stock D, Knight JA, Raboud J, Cotterchio M, Strohmaier S, Willett W, et al. Rotating night shift work and menopausal status. Hum Reprod. 2019;34(3):539–48.

[149] Fischer D, Lombardi DA, Marucci-Wellman H, Roenneberg T. Chronotypes in the US - influence of age and sex. PLoS One. 2017;12(6):e0178782.

[150] van de Ven HA, van der Klink JJ, Vetter C, Roenneberg T, Gordijn M, Koolhaas W, et al. Sleep and need for recovery in shift workers: do chronotype and age matter? Ergonomics. 2016;59(2):310–24.

[151] Bhattacharjee RR, Davis S. The impact of chronotype on melatonin levels among shift workers. Occup Environ Med. 2014;71(3):195–200.

[152] Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, et al. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. Ann Oncol. 2013;24(11):2724–32.

[153] Dun A, Zhao X, Jin X, Wei T, Gao X, Wang Y, et al. Association between night-shift work and cancer risk: updated systematic review and meta-analysis. Front Oncol. 2020;10:1006.