Night Shift Work and Breast Cancer Risk: A Meta-analysis of Observational Epidemiological Studies

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ABSTRACT

Night Shift Work and Breast Cancer Risk: A Meta-analysis of Observational Epidemiological Studies

Background: Previous observational epidemiological studies have reported the association between night shift work (NSW) and several site-specific cancers such as breast, prostate, and lung cancer. However, the association between night shift work and the risk of breast cancer (BC) remains inconsistent. This study aimed to investigate those associations by using a meta-analysis of observational epidemiological studies.

Methods: We searched PubMed and EMBASE using keywords related to this topic from inception till November 2020. The pooled effect sizes such as odds ratio (OR), hazard ratio (HR), or relative risk (RR) with 95% confidence interval (CI) were calculated using a random-effects model.

Results: In the meta-analysis of a total of 32 observational studies including 13 case-control studies, 4 nested case-control studies, and 15 cohort studies, NSW significantly increased the risk of BC (OR/RR/HR, 1.11; 95% CI, 1.04 to 1.20; I^2 = 72.4%). In the subgroup meta-analysis by type of study, NSW was also associated with the increased risk of BC in case-control studies (OR, 1.34; 95% CI, 1.17 to 1.53; I^2 = 63.8%). However, no significant association was found in both nested case-control studies (OR, 1.14; 95% CI, 0.89 to 1.46; I^2 = 65.8%) and cohort studies

(RR/HR, 0.98; 95% CI, 0.93 to 1.03; I^2 = 25.3%). Besides, there was no significant association between NSW for over 20 years and the risk of BC (OR/RR/HR, 1.03; 95% CI, 0.95 to 1.11; I^2 = 36.6%, n = 14).

Conclusion: Given that cohort studies provide higher evidence than case-control studies, there is no association between NSW and the risk of BC. Further large prospective cohort studies are warranted to confirm these associations.

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Abbreviations

NSW: night shift work

NSWer (s): night shift worker (s)

BC: breast cancer

CVDs: cardiovascular diseases

T2DM: type 2 diabetes mellitus

CI: confident interval

RR: relative risk

IARC: International Agency for Research on Cancer

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: International Prospective Register of Systematic Reviews

EMBASE: Excerpta Medica dataBASE

MeSH: Medical Subject Heading

OR: odds ratio

HR: hazard ratio

NOS: Newcastle-Ottawa Scale

1. Introduction

1.1 Overview of night shift work

According to the definition of the International Labor Office, shift work is a method of arrangement of working time in which people take turns working so that the organization can run longer than the time of individual workers [1]. Generally, in the scientific literature, the term "shift work" contains any working hours outside of the standard working hours (7-8 AM to 5-6 PM) [2, 3]. Shift work includes night shift, overnight shift, late evening shift, and early morning shift [4].

The definition of NSW is varied between countries. Table 1 shows the definitions of NSW and NSWer in countries [1].

Table 1. Definitions of night shift work and night shift worker in some countries

Country	Night shift work	Night shift worker
United State	Period between 22:00 and 05:00	
United Kingdom	Period lasting not less than 7 hours, and which includes the period between midnight and 05:00	Works at least 3 hours of daily working time includes the period during night time
France	Period between midnight	Works usually at least 2 times

	and 05:00	per week for at least 3 hours over the night work period
Germany	Night time: the time between 23:00 and 06:00 (in case of bakers between 22:00 and 05:00). Night work: all work which occupies more than 2 hours of night time	Workers who usually work nights on rotating shifts schedules, or work at night for not less than 48 days in a calendar year
Finland	Work carried out between 23:00 and 06:00	Works shift with at least 3 hours of duty between 23:00 and 06:00
Netherland	Cover all or part of the period from midnight to 06:00	
Sweden	Period between midnight and 05:00	Works at least 3 hours of daily work during night time, or a worker that most likely will work at least 38% of annual work during the night
Spain	Period between 22:00 and 06:00	Works at night at least 3 hours of daily working time
Australia	Period between 22:00 and 05:00	Works at least 3 hours between 22:00 and 05:00 on at least 48 nights per year

NSW is also called overnight shift, third shift, “nine-to-five” workday, or

graveyard shift [3, 5, 6]. NSW often associates with essential public services (e.g. hospitals, police, and fire brigade), industries with 24-hour operation (e.g. transportations and manufacturing), and consumer service industries (e.g. supermarkets, petrol stations, and flight attendants) [7].

In the 21st century, the landscape of shift work is changing rapidly. In recent decades, the advent of new technologies and the fierce competition among companies as well as countries have required the attendance of humans in the work processes during the 24-hour day to optimize labor productivity [8]. Also, with globalization and the time zone deviations, some industries that did not have shift work before such as the finance and banking industry are now considering extended working hours [9]. In addition, the extension in demand for basic services of the general population indicated the need of working outside office hours [8]. Kreitzman gave the term "the 24-hour society" to represent a society in which people are both consumers and producers at any time both day and night [10]. According to the Sixth European Working Conditions Survey, approximately 18% of the workforce reported engaging in NSW (more than two hours of work between 22:00 - 05:00) at least once per month in 2010, and this number increase to 19% in 2015 [11]. In Korea, it is estimated around 10.2 - 14.5% of the workers who engaged in night shift [12]. NSW is an indispensable part of modern society. With a growing number of NSWers, studies of NSW might help to provide evidence for epidemiologists give policies to reduce its effects on workers' health.

1.2 Night shift work and its impact on health

Numerous studies have reported the impact of NSW on both physical health and mental health [9, 13].

1.2.1 Physical health

In physical health, NSW affects circadian rhythms and sleep, increases the risk of gastrointestinal disorders, cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), and some types of cancer.

NSW disturbs the time of sleep therefore it changes circadian rhythms and impacts on both sleep quantity and sleep quality [6]. Several studies have reported reduction in sleep quality and sleep duration, longer sleep latency, and sleep disturbances in NSWers [14-16]. In 2016, a study indicated that the prevalence of police officers working night shift who had poor sleep quality was 70%, compared with those on the day shift [17]. Garde et al. showed that nurses on mixed night shift slept 2 hours and 37 minutes less on workdays compared to days off [18]. Another study suggested that NSW was associated with an increase of long sleep (more than 9 hours per 24 hours). This increase was explained by a higher need for recovery sleep in NSWers [19].

Following sleep disturbance, gastrointestinal disorders in NSWers were reported second-most [20, 21]. Workers on the night shift might change their timetable of meals (adjusted schedule to fit shift work), frequency of eating

(addition night meal or eating after shift work), as well as composition and quality of meals (cool food, canned food, and food with more fats and carbohydrates) [22, 23]. Several studies reported that the risk of gastrointestinal disorders in NSWers was higher than in people having day shifts [20, 22]. The common gastrointestinal diseases in people having NSW included heartburn, constipation, diarrhea, bloating, difficult indigestion, pyrosis, gastroduodenitis, peptic ulcer, and irritable bowel syndrome [23-26].

Metabolic syndrome included at least three of five medical conditions: abdominal obesity, hyperglycemia, high serum triglycerides, hypertension, and low serum high-density lipoprotein [27]. Several studies showed that NSW increased the risk of metabolic syndrome [14, 28, 29]. Circadian disruption, reduction in sleep quality, change in food consumption were reported as causes of metabolic syndrome Besides, metabolic syndrome is related with the risk of CVDs and T2DM [27, 30].

In 2018, two meta-analyses of observational studies on the association between NSW and risk of CVDs were published [31, 32]. Both of them showed that NSW significantly increased the risk of CVDs, but the curves representing a dose-response relationship were non-linear [31, 32]. However, the causal relationship between NSW and CVDs remains unclear [33]. It has been suggested that the association between NSW and CVDs might be because of the combination of sleep deprivation, circadian disruption, disturbed cardiac autonomic control, stressful work environment, and lifestyle changes [33].

Moreover, the increases in some risk factors of CVDs such as smoking [34], obesity [35, 36], and dyslipidemia [37] were reported in NSWers. These factors might be confounders in the relationship between NSW and risk of CVDs [38].

Many prospective cohort studies suggested that NSW increased T2DM risk [39-41]. In addition, two prospective cohort studies in healthcare staffs (Nurses' Health Study I and II) indicated that the more night shifts per month, the higher T2DM risk [42]. The latest meta-analysis concluded that NSW increased 10% the risk of T2DM (95% confidence interval (CI), 1.05-1.14) [43]. This increase might be due to the change in eating habits and sleeping time leading to glucose metabolism disorders [44]. An experimental study on humans showed that circadian disruption can induce a disturbance in the system of glucose-insulin regulation [45].

1.2.2 Mental health

Besides the risk of physical disorders, people engaging in NSW have had to be faced with mental disorders such as stress, anxiety, depression, bipolar disorder, as well as having suicidal ideation [46-48]. Notably, the risk of depression in women higher than in men [49, 50]. In addition, Turchi et al.'s study reported that NSW reduced the quality of life among nurses, around 48% of nurses did not feel sense of well-being [51].

In addition to health problems, NSWers are confronted with a variety of family and social problems [52]. Because most family and social activities

operate to follow the rhythms of the general population, it is difficult to balance NSW and family duty (housework, take care of their offspring and spouse) [9].

1.3 Night shift work and the risk of cancer

In June 2019, a group including 27 scientists was convened by the International Agency for Research on Cancer (IARC) to re-evaluate the carcinogenicity of NSW. In conclusion, they classified "night shift work" as a probably carcinogenic factor to humans (Group 2A) because of the sufficient proofs in experimental animal models, but the inadequate evidence in humans [53]. In 2007, IARC categorized "shiftwork involving circadian disruption" into Group 2A [54]. The change of the terminology from "shiftwork involving circadian disruption" to "night shift work" described better the exposure and reflected the main evidence base on human cancer studies [53, 55].

There was inconsistency in the conclusions in articles researching the association between NSW and cancer risk. Some observational epidemiological studies showed that NSW increased the risk of breast [56, 57], prostate [58, 59], ovarian [60], and colorectal cancer [61, 62]. Conversely, other studies found that NSW was not associated with an increase in the risk of breast [63, 64], prostate [65, 66], ovarian [59, 67], colorectal [68, 69], and stomach cancer [70]. In 2020, a meta-analysis including six case-control studies and twelve cohort studies reported that there was no association between NSW and prostate cancer risk (OR, 1.07, 95% CI, 0.99 to 1.15) [71]. In 2015, Wang et al. conducted a

meta-analysis and suggested that NSW increased the risk of colorectal cancer (OR, 1.32; 95% CI, 1.12 to 1.55) [72]. However, a subgroup analysis by study design showed an increase in the risk of colorectal cancer only in case-control studies (OR, 1.63; 95% CI, 1.32 to 2.01), but not in cohort studies (OR, 1.08; 95% CI, 0.98 to 1.32) [72]. The reduction in the melatonin synthesis and the dysfunction of circadian genes were underlying mechanisms that have been proposed to explain an increase in cancer risk in NSWers [73-76]. Detail of these mechanisms is mentioned in the discussion.

1.4 Night shift work and the risk of breast cancer

According to GLOBOCAN 2018, BC has the highest in the numbers of new cases and deaths among all types of cancers in women worldwide (24.2% and 15.0%, Figure 1) [77]. Because risk prediction models are important for the prevention of BC [78], it is essential to study risk factors of this cancer. Although age, genes, and alcohol have already been proven to be important risk factors for the formation and expansion of BC [79], other risk factors such as NSW remain controversial [80].

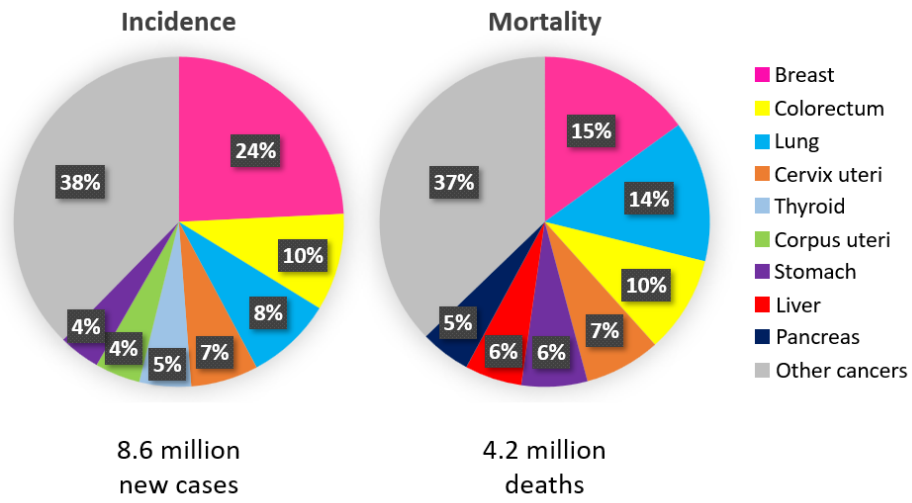

Figure 1. The numbers of new cases and deaths in all cancer in women worldwide (Source: GLOBOCAN - Global Cancer Statistics 2018) [77]

Previous observational epidemiological studies have reported different findings on the association between NSW and the risk of BC. Some studies indicated that NSW increased the risk of BC [81-84], whereas others found no significant association between them [85-87]. Also, several meta-analyses on this topic have reported inconsistent findings [64, 88, 89]. In 2015, He et al. conducted a study including 15 studies (11 case-control studies and 4 cohort studies) and concluded that NSW increased the risk of BC about 19% (95% CI, 1.08-1.32) [89]. In 2016, a meta-analysis including 10 cohort studies demonstrated that NSW has little effect or no effect on BC risk (relative risk (RR), 0.99; 95% CI, 0.95-1.03) [64]. However, this study did not conduct any subgroup meta-analysis. Since 2016, at least 12 epidemiological observational studies including 4 case-control studies and 8 cohort studies have been

published [12, 57, 90-98]. In these 12 studies, there were three studies that indicated a significant association between NSW and BC risk [57, 90, 91] and nine studies found no association between them [12, 92-98].

1.5 Aims of this study

The findings of the association between NSW and BC risk still inconsistent. Therefore, we conducted this study to investigate the associations between NSW and the risk of BC in women by using a comprehensive meta-analysis of observational epidemiological studies including both case-control studies and cohort studies.

2. Materials and Methods

2.1 Study protocol and registration

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The PRISMA provides a list of items that should be reported in systematic reviews and meta-analyses. The PRISMA checklist of this study is shown in Appendix A.

The protocol of this study was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) in August 2019. PROSPERO is an international database of registered systematic reviews in many fields that have a health-related outcome such as public health, health care, welfare, crime, justice, and education. PROSPERO was formed with the aim of providing a list of systematic reviews registered in advance in order to shun duplication and reduce the probable bias report. PROSPERO is developed by the Centre for Reviews and Dissemination and funded by the National Institute for Health Research. The protocol of our study was approved in January 2020 with the registration number: CRD42020147114. The record of protocol registration was described in Appendix B.

2.2 Literature search strategy

We searched for eligible studies from PubMed and EMBASE. PubMed is a free resource that aims to support the search for peer-reviewed biomedical and sciences literature to improve global and personal health. PubMed was created and is managed by the National Center for Biotechnology Information, which was located at the National Institutes of Health. Available to the public online since 1996, till now, this database includes more than 30 million articles and abstracts in the biomedical field. In addition, PubMed covers the National Library of Medicine journal citation database [99]. EMBASE, stands for Excerpta Medica dataBASE, which is a database that contains biomedical and pharmacological published studies. EMBASE was developed by Elsevier in 1974, till now on, it has encompassed approximately 32 million records from about 8,500 journals. [100].

We selected keywords based on the Medical Subject Heading (MeSH) Description Data. The search keywords related to current topic are as follows: “night shift work”, “rotating shift work”, “shift work schedule”, and “night work” for exposure; “breast cancer”, “breast tumor”, “breast carcinoma” for outcome. Details of the search strategies was shown in Table 2. We conducted an exhaustive search for eligible studies that were published from inception till November 2020.

Table 2. Terms and text words in searching in PubMed and EMBASE

Database	Terms	Syntax
PubMed		
Exposure	night shift work, rotating shift work, shift work schedule, shift work, night work	(night shift work OR rotating shift work OR shift work schedule OR shift work OR night work) AND (breast cancer OR breast tumor OR breast carcinoma)
Outcome	breast cancer, breast tumor, breast carcinoma	
EMBASE		
Exposure	night shift work, rotating shift work, shift work schedule, shift work, night work	('night shift work' OR 'rotating shift work' OR 'shift work schedule' OR 'shift work' OR 'night work') AND ('breast cancer' OR 'breast tumor' OR 'breast carcinoma')
Outcome	breast cancer, breast tumor, breast carcinoma	

2.3 Eligibility criteria

Studies were selected if they (i) are a case-control study, a nested case-control study, or a cohort study, (ii) investigated the association between NSW and the risk of BC in women, (iii) reported the outcome measures using adjusted odds ratio (OR), hazard ratio (HR), or RR with its 95% CI. We only included the

original articles in our study and excluded animal experiment studies. When more than one article shared data, the most comprehensive study or the first published one was included.

2.4 Selection of relevant studies and data extraction

Two of the authors (Nhung Thi Hong Van and Seung-Kwon Myung) independently evaluated and selected studies that met the selection criteria. Discrepancies between evaluators were solved by further discussion. In each study, we extracted the data regarding the following items: study name, first author, year of publication, study design, region, period of enrollment, characteristics of population (number of cases and controls, age, average follow-up period, and occupation), definition of night shift, shift schedule and comparisons, duration of NSW, follow-up rate (in nested case-control studies and cohort studies) or response rate (in case-control studies), menopausal status, OR, RR, or HR with its 95% CI, and adjusted variables.

2.5 Assessment of methodological quality

To assess the methodological quality of included studies, we used the Newcastle Ottawa Scale (NOS) for observational studies [101]. The numbers of stars range from 0 to 9 and the stars were divided up among three subscales: selection of studies (0 to 4 stars), comparability (0 to 2 stars), and exposure (0

to 3 stars). A higher score indicates a better study in quality. In the current study, a study given the number of stars greater than the average score of the studies in the same type was considered as a high-quality study because a standard cut-off score has not been established.

2.6 Main analysis and subgroup meta-analyses

In the main analysis, we investigated the association between NSW and the risk of BC by using adjusted ORs, RRs, or HRs with their 95% CIs. We also conducted subgroup meta-analyses by types of study (case-control study, nested case-control study, and cohort study), shift schedule (fixed, rotating, and mixed), region (Europe, North America, Asia, and Australia), type of occupation (nurse, working in industry, and other occupations), menopausal status (premenopausal and postmenopausal), follow-up rate or response rate (less than 80% and 80% or more), methodological quality (high quality and low quality), and duration of night shift (less than 10 years, 10 to 20 years, and more than 20 years).

2.7. Statistical analyses

From individual studies, we collected adjusted ORs, RRs, or HRs and their 95% CIs to calculate a pooled effect size with its 95% CI. Because individual studies involved different populations, we used a random-effects model with the Der Simonian and Laird method [102]. To examine heterogeneity in results

across studies, we used Higgins I^2 which calculates the percentage of total variation across studies. The equation of Higgins I^2 was described as follow:

$$I^2 = \frac{Q-df}{Q} \times 100(\%),$$

where Q is Cochran's heterogeneity statistic and *df* is the degree of freedom. If the value of I^2 is smaller than 0, it is put equal to 0. The I^2 value ranges from 0% to 100%, respectively from no heterogeneity to maximal heterogeneity. In general, if I^2 value is greater than 50%, it supposed to be substantial heterogeneity [103].

In this study, publication bias was evaluated by using the Begg's funnel plot and Egger's test. If publication bias exists, the Begg's funnel plot will be asymmetrical or the p-value of Egger's test will be lower than 0.05. If two tests show inconsistent results, the results from Egger's test will be adopted because detection bias via observe the funnel plot might be imprecise and misleading [104]. To evaluate the dose-response relationship between NSW and BC risk, we used a generalized weighted least squares regression model based on the Greenland and Longnecker method [105]. Statistical analyses were performed using the Stata SE version 14.0 software package (Stata Corp., College Station, Texas, USA).

3. Results

3.1 Selection of relevant studies

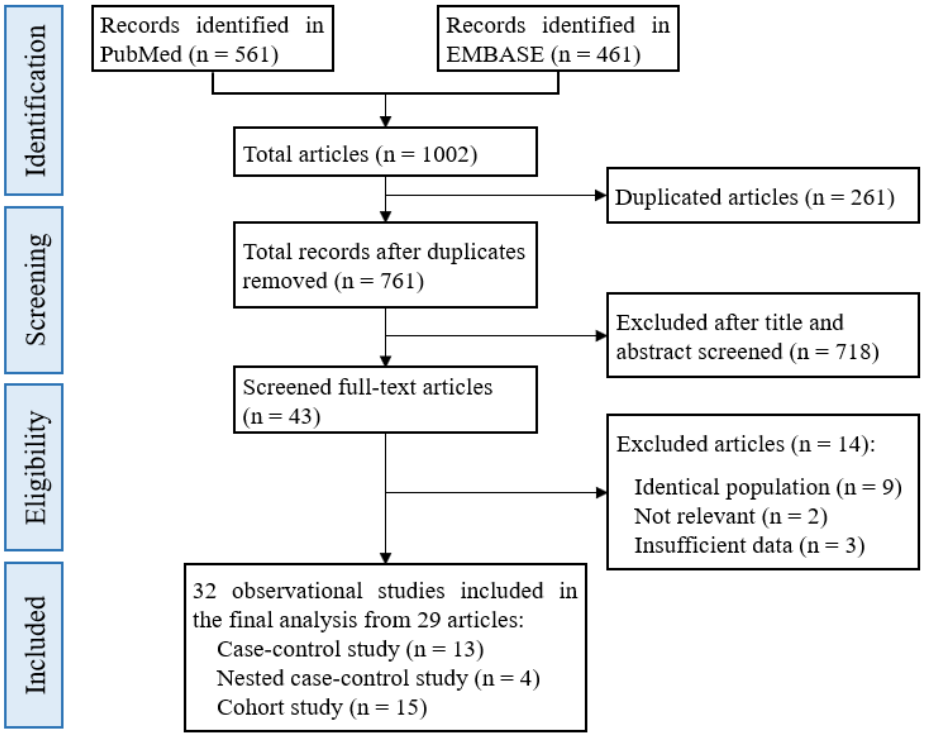

Figure 2. PRISMA flow diagram of the meta-analysis

A flow diagram for the selection process of relevant studies is shown in Figure 2. A total of 1,002 articles were identified by searching two databases: 561 articles from PubMed and 461 articles from EMBASE. After removing 261 duplicate articles, two authors independently screened first round by reading titles and abstracts of 761 articles, and then excluded 718 articles that did not meet the predetermined selection criteria. After that, we reviewed full texts of

the remaining 43 articles, further excluded 14 articles and included 29 articles. Among 14 excluded articles, nine studies shared the same population with other articles, two studies not relevant to this topic, and three studies reported insufficient effect size or 95% CI. Finally, from 29 selected articles, a total of 32 studies with 13 case-control studies, 4 nested case-control studies, and 15 cohort studies were included in the final analysis.

3.2 Characteristics of the studies included in the final analysis

Table 3 shows general characteristics of the 32 studies included in this meta-analysis [5, 12, 56, 57, 63, 64, 81-87, 90-98, 106-112]. From case-control studies and nested case-control studies, we identified a total of 47,942 participants including 20,885 cases and 27,057 controls. In cohort studies, there were a total 2,414,755 participants, of which 58,896 women were diagnosed with BC. The regions where the individual studies had been conducted were as follows: Europe (n = 17), North America (n = 9), Asia (n = 5), and Australia (n = 1). All participants were women aged between 16 and 85 years old. In cohort studies, the average follow-up period ranged from 2.6 to 18.2 years.

Table 3. General characteristics of observational epidemiological studies included in the analysis

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2001 Davis [5]	Case-control study	North America 1992-1995	767 cases 743 controls Age: 20-74 years old	Beginning work after 7:00 PM and leaving work before 9:00 AM	Mixed, never vs ever	1.6 (1.0-2.5)	Parity, family history of breast cancer (mother or sister), oral contraceptive use (ever), and recent (<5 years) discontinued use of hormone replacement therapy
2001 Hansen [81]	Case-control study	Europe NA	7035 cases 7035 controls Age: 30-54 years old	Work at least half a year in trades with predominantly night work	Fixed, never vs. > 6 months	1.5 (1.3-1.7)	Age, social class, age at birth of first child, age at birth of last child, and number of children
2006 Lie [82]	Nested case-control study	Europe 1960-1982	537 cases 2,143 controls 44,835 women nurses who graduated from Norwegian school between 1914- 1980, and were alive in 01/1953 or born later	Night shift in nurses	Rotating, never vs. ≥ 30 years	2.21 (1.10-4.45)	Total employment time as a nurse and parity

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2006 O'Leary [106]	Case-control study	North America 1996-1997	487 cases 509 controls Age: <75 years old Long Island Breast Cancer Study Project	Evening shift: end at 2:00 AM. Over-night shift: start at 7 PM	Mixed, never vs. ever	1.04 (0.79-1.38)	Age at the reference date, parity, family history, education, and history of benign breast disease
2010 Pesch [85]	Case-control study	Europe 2004-2007	857 cases 892 controls Age: <80 years old Gene Environment Interaction and breast Cancer (GENICA)	Working the fulltime period between 00:00 AM and 05:00 AM	Mixed, never vs ever	0.91 (0.55-1.49)	Hormone replacement use, family history of breast cancer, and number of mammograms
2010 Pronk [63]	Cohort study	Asia 1996-2007	73,049 persons 717 cases Age: 40-70 years old Shanghai Women's Health Study. Average follow-up period: 9.0 years	Working after 10:00 PM at least 3 times a month for over 1 year.	Mixed, never vs. ever	1.0 (0.9-1.2)	Age, education, family history of breast cancer, number of pregnancies, age at first birth, and occupational physical activity
2011 Lie [86]	Nested case-control study	Europe 1990-2007	699 cases 895 controls 49,402 female nurses	A shift that lasted from at least 00:00 PM until 6:00 AM	Mixed, never vs. ≥ 12 years	1.3 (0.9-1.8)	Age, period of diagnosis, alcohol consumption parity, history of breast cancer in mother or sister

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2012 Hansen [87]	Nested case-control study	Europe 1990-2003	141 cases 551 controls 18,551 female military employees born in 1929-1968	05:00 PM to 9:00 AM, not including overtime, for at least 1 year	Mixed, never vs. ever	1.4 (0.9-2.1)	Age, age at menarche, years of education, number of childbirths, hormone replacement therapy, tobacco smoking status, and occasional sunbathing frequency
2013 Fritschi [107]	Case-control study	Australia 2009-2011	1,201 cases 1,783 controls Age: 18-80 years old The Breast Cancer Environment and Employment Study (BCEES)	Working between 00:00 AM and 05:00 AM	Mixed, never vs ever	1.16 (0.97-1.38)	Light at night, phase shift, sleep disruption, poor diet, lack of physical activity, little time outdoors, and age
2013 Grundy [83]	Case-control study	North America 2005-2010	1,134 cases 1,179 controls Age: 20-80 years old	Started or ended between 11:00 PM and 7:00 AM	Mixed, never vs. ≥ 30 years	2.21 (1.14-4.31)	Age and center
2013 Knutsson [84]	Cohort study	Europe 1992-2003	94 cases 4,036 persons Age: 19-70 years old The WOLF (Work,	From 10:00 PM to 06:00 AM	Mixed, never vs. ever	2.02 (1.03-3.95)	Number of children and alcohol consumption

			Lipids, and Fibrinogen). Average follow-up period: 12.4 years				
2013 Menegaux [108]	Case-control study	Europe 2005-2008	1,232 cases 1,317 controls Age: 25-75 years old	Overnight (more than 6 hours in period 11pm – 5 am). Late evening (ending 11pm – 3am). Early morning (starting 3am - 5am)	Mixed, never vs ever	1.27 (0.99-1.64)	Age, study area, parity, age at first full-term pregnancy, family history of breast cancer, age at menarche, BMI, tobacco, alcohol, and hormone replacement therapy
2014 Koppes [109]	Cohort study	Europe 1996-2009	2531 cases 285,723 in population Age: ≥ 15 years old Labor Force Survey data. Average follow-up period: 9 years	Working from 00:00 PM to 06:00 AM	Mixed, never vs. ever	0.87 (0.72-1.05)	Night work, age, origin, children occupation, in household, education, job tenure, and contractual working hour
2015 Akerstedt [110]	Cohort study	Europe 1998-2010	13,656 persons 463 cases Age: ≤ 60 years old The Swedish Twin Registry. Average	Working from 10:00 PM to 06:00 AM	Mixed, never vs. ever	0.94 (0.73-1.22)	Age, education level, tobacco consumption, BMI, having children, coffee consumption, previous cancer, and

			follow-up period: 8.7 years				use of hormones including oral contraceptives
Study	**Type of study**	**Region Years enrolled**	**Population**	**Definition of night shift**	**Type of night shift and comparisons**	**OR/RR/HR (95% CI)**	**Adjusted variables**
2015 Li [111]	Nested case-control study	Asia	1709 cases 4,780 controls	Working between 00:00 AM and 05:00 AM	Mixed, never vs. > 27.67 years	0.88 (0.74-1.05)	Age at the beginning of follow-up
2015 Wang [56]	Case-control study	Asia 2010-2012	661 cases 714 controls	Working between 00:00 AM and 06:00 AM	Mixed, never vs ever	1.43 (1.05-1.72)	Age, education, BMI, age at menarche, menopausal status, breastfeeding, parity, physical activity, family history of breast cancer, and other sleep factors
2016 Papantoni-ou [112]	Case-control study	Europe 2008-2013	1,708 cases 1,778 controls Age: 20-85 years old The multi case-control study (MCC-Spain study)	Working between 00:00 AM and 06:00 AM	Mixed, never vs ever	1.18 (0.97-1.43)	Age, center, educational level, parity, menopausal status, family history of breast cancer, smoking status, oral contraceptive use, BMI, leisure-time

							physical activity, sleep duration, and alcohol consumption
2016 Travis (EPIC-Oxford) [64]	Cohort study	Europe 2010-2013	22,559 persons 181 cases Age: 35-69 years old EPIC-Oxford (The Oxford component of the European Prospective Investigation into Cancer and Nutrition) population. Average follow-up period: 3.12 years	At least 1 night per month or 12 nights per year, for at least 1 year	Mixed, never vs. ever	1.07 (0.71-1.62)	Deprivation, parity and age at first birth, BMI, alcohol intake, smoking, married or living with a partner, age at menarche, strenuous physical activity, use of oral contraceptives, and use of postmenopausal HT
2016 Travis (MWS) [64]	Cohort study	Europe 2010-2013	522,246 persons 4,809 cases Age: 50-64 years old The Million Women Study. Average follow-up period: 2.6 years	Between 00:00 AM and 06:00 AM, at least 3 nights per month, for at least 1 year	Mixed, never vs. ever	1.00 (0.92-1.08)	Socioeconomic status, parity and age at first birth, alcohol, strenuous physical activity, family history of breast cancer, age at menarche, oral contraceptive, smoking, living with a partner, BMI, use of menopausal HT

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2016 Travis (UK Biobank) [64]	Cohort study	Europe 2008-2012	251,045 persons 2,720 cases Age 40-69 years old UK Biobank population. Average follow-up period: 3.8 years	Current job involves night shift work (sometimes, usually or always)	Mixed, current vs not current having night shift work	0.78 (0.61-1.00)	Deprivation, parity and age at first birth, BMI, alcohol, smoking, family history of breast cancer, living with a partner, age at menarche, vigorous physical activity, use of oral contraceptives, and postmenopausal HT use
2017 Jorgensen [92]	Cohort study	Europe 1993-2013	18,015 persons 204 cases Age: ≥ 44 years old The Danish nurse cohort (DNC) Average follow-up period: 17.6 years	Working between 11:00 PM and 07:00 AM	Rotating, never vs. ever	1.20 (0.70-2.08)	Age, smoking, pack-years, physical activity, BMI, alcohol consum-ption, diet, pre-existing diseases, self-reported health, stressful work environment, marital status, and female reproductive factors
2017 Vistisen [93]	Cohort study	Europe 2007-2012	155,540 persons 1245 cases Age: ≥ 8 years old	Working between 00:00 AM and 05:00	Mixed, never vs. ever	0.90 (0.80-1.01)	Age, age at birth of the first child, number of births, family history

			The Danish Working Hour Database	AM			of breast or ovarian tumor, hormone replacement therapy, oral contraception, medication-related to alcoholism, and
2017 Wegrzyn (NHS) [94]	Cohort study	North America 1988-2012	78,516 persons 5971 cases Age: 30-55 years old The Nurses' Health Studies	Night shift in nurses	Rotating, never vs. ≥ 30 years	0.95 (0.77-1.17)	Age, height, BMI, BMI at age 18, age at menarche, age at first birth and parity combined, age at menopause combined, breastfeeding, use of menopausal HT, duration of estrogen alone menopausal HT, duration of estrogen and progesterone menopausal HT, first-degree family history of breast cancer, history of benign breast disease, physical activity, alcohol consumption, and mammography use
2017 Wegrzyn (NHS2) [94]	Cohort study	North America 1989-2013	114,559 persons 3,570 cases Age: 25-42 years old The Nurses' Health Studies	Night shift in nurses	Rotating, never vs. ≥ 20 years	1.40 (1.00-1.97)	

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2018 Yang [57]	Case-control study	Asia 2013-2016	401 cases 401 controls Age: 18-74 years old The Jiujiang breast cancer study (JBCS)	NA	Mixed, never vs ever	1.38 (1.04-2.71)	Age, education, family income, number of live births, use of menopausal hormones, occupation, menopausal status, age at menarche, age at first birth, marital status, family history of breast cancer, smoking, alcohol drinking, fruit and vegetable consumption, regular physical activity, BMI, and other sleep variables (sleep duration, sleep quality, LAN, night/shift work, and sleep medication use)

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2019 Bustamante-Montes [90]	Case-control study	North America	101 cases 101 controls The Instituto de Seguridad Social del Estado de Mexico y Municipios	Working from 09:00 PM to 07:00 AM for at least one year	Mixed, never vs. ever	8.58 (2.19-33.8)	Age at onset of menarche, menopausal status, lactation history, BMI, and smoking status
2019 Jones [95]	Cohort study	Europe 2003-2014	102,869 persons 2,059 cases Age: ≥16 years old The Generations Study. Average follow-up period: 9.5 years	From 10:00 PM to 07:00 AM	Mixed, never vs. ever	1.00 (0.86-1.15)	Age, birth cohort, time since recruitment to cohort, benign breast disease, family history of breast cancer, socio-economic, birth weight, height at age 20, age at menarche, BMI at age, parity, breast-feeding, age started smoking, alcohol consumption, contraceptive use, BMI, physical activity, menopausal HT use, menopausal status, and age at menopause

Study	Type of study	Region Years enrolled	Population	Definition of night shift	Type of night shift and comparisons	OR/RR/HR (95% CI)	Adjusted variables
2019 Pham [12]	Case-control study	Asia 2012-2018	1,721 cases 1,721 controls Age: ≥ 20 years old The Breast Cancer or Health Examination Center at National Cancer Center	Working in night shifts regularly between 09:00 PM and 08:00 AM for at least 2 months	Mixed, never vs. ever	1.11 (0.89-1.40)	Age, educational level, age at birth of first child, BMI, age at menarche, alcohol consumption, use of hormone treatment, smoking, and family history of breast cancer
2020 Harris [97]	Cohort study	North America	939,520 women 30,775 cases The Canadian Census Health and Environment Cohort (CanCHEC) Average follow-up period: 18.2 years	NA	Mixed, un-exposure (0-5% probability) vs. high (>50%) probability of exposure	0.99 (0.92-1.05)	Age, provincial region, education, and parity (numbers of live births)
2020 McNeil [98]	Cohort study	North America	13,457 women 366 cases Alberta`s Tomorrow Project (ATP) cohort Average follow-up period: 10.9 years	NA	Rotating, never vs. ever	0.87 (0.61-1.25)	Age, BMI, the highest level of education, total household income, employment status, ethnicity, marital status, smoking status, presence of at least one

							medical condition/co-morbidity, family history of cancer, and menopausal status
2020 Szkiela [91]	Case-control study	Europe 2015-2019	494 cases 515 controls Age: ≥ 35 years old	NA	Mixed, never vs. ever	2.20 (1.57-3.08)	High BMI, smoking, early menstruation, late menopause, pregnancy history, age, place of living, and education
2020 Sweeney [96]	Cohort study	North America	48,451 persons 3191 cases Sister Study cohort Average follow-up period: 9.1 years	Night shift: ≥ 1 hours between 12:00 – 2:00 AM ≥ 1 job with rotating shifts	Rotating, never vs. ever	1.08 (0.92-1.27)	Age, marital status, race/ethnicity, education, and parity

Abbreviations: NA, not available; OR. Odds ratio; RR, relative risk; HR, hazard ratio; CI, confident interval; BMI, body mass index; HT, hormone therapy.

3.3 Methodological quality assessment

The assessment of the methodological quality of each individual study is shown in Appendix C and is summarized in Table 4. The numbers of stars ranged from 6 to 9. Case-control study, nested case-control study, and cohort study had an average score of 7.46, 7.25, and 7.27, respectively. Based on the mean score of each type of study, 12 studies were regarded as high-quality studies, and the remaining 20 studies low-quality studies.

Table 4. Summary of methodological quality assessment by the NOS

	Case-control study	Nested case-control study	Cohort study	All study
6 stars	1	1	1	3
7 stars	5	2	10	17
8 stars	4	0	3	7
9 stars	3	1	1	5
Average	7.46	7.25	7.27	
High quality	7	1	4	12
Low quality	6	3	11	20

3.4 Main analysis

3.4.1 Meta-analysis of all studies

Overall, NSW statistically significantly increased the risk of BC in the random-effects model meta-analysis of all 32 observational epidemiological studies (OR/RR/HR, 1.11; 95% CI, 1.04 to 1.20; I^2 = 72.4%, Figure 3).

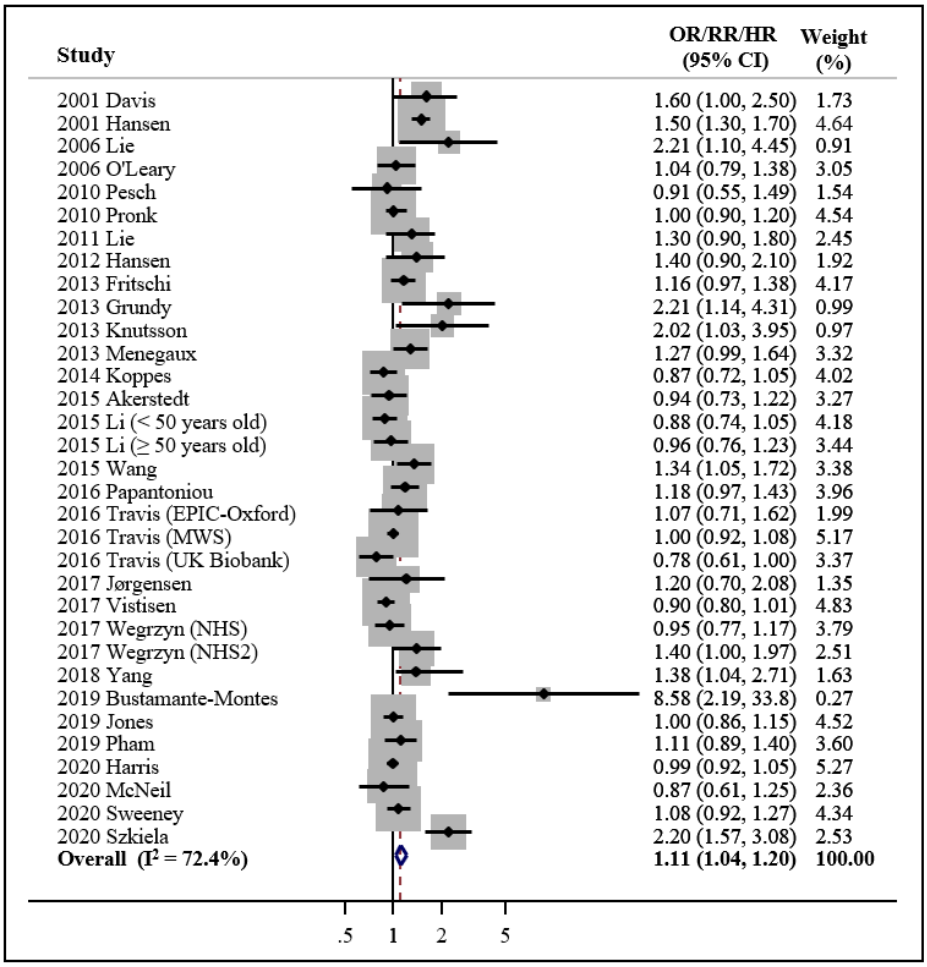

Figure 3. Association between night shift work and the risk of breast cancer in a random-effects model meta-analysis of all studies (n = 32). OR, Odds

Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

3.4.2 Meta-analysis by type of study design

In the subgroup meta-analysis by type of study, NSW was associated with the increased the risk of BC in case-control studies (OR, 1.34; 95% CI, 1.17 to 1.53; I^2 = 63.8%; n = 13, Figure 4). However, no significant association between them was found in both nested case-control studies (OR/HR, 1.14; 95% CI, 0.89 to 1.46; I^2 = 65.8%; n = 4, Figure 5) and cohort studies (RR/HR, 0.98; 95% CI, 0.93 to 1.03; I^2 = 25.3%; n = 15, Figure 6). Compared with the result of meta-analysis in case-control studies, the risk of BC decreased but the association remained significant when we included both case-control studies and nested case-control studies (OR/HR, 1.29; 95% CI, 1.13 to 1.46; I^2 = 70.7%; n = 17, Figure 7).

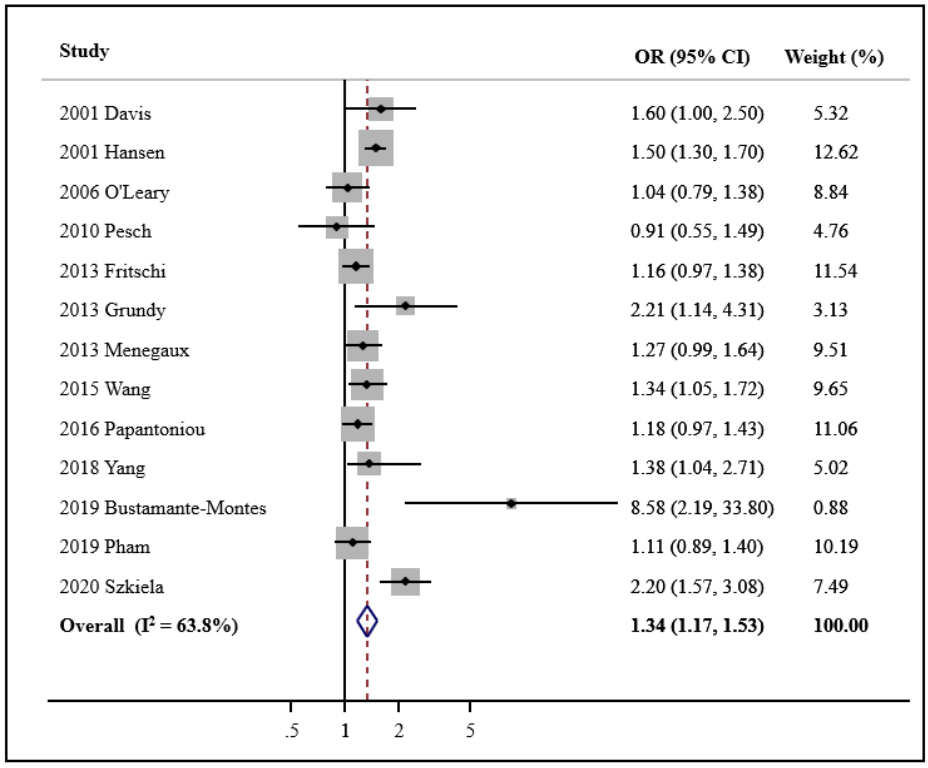

Figure 4. Association between night shift work and the risk of breast cancer in case-control studies (n = 13). OR, Odds Ratio; CI, Confidence Interval

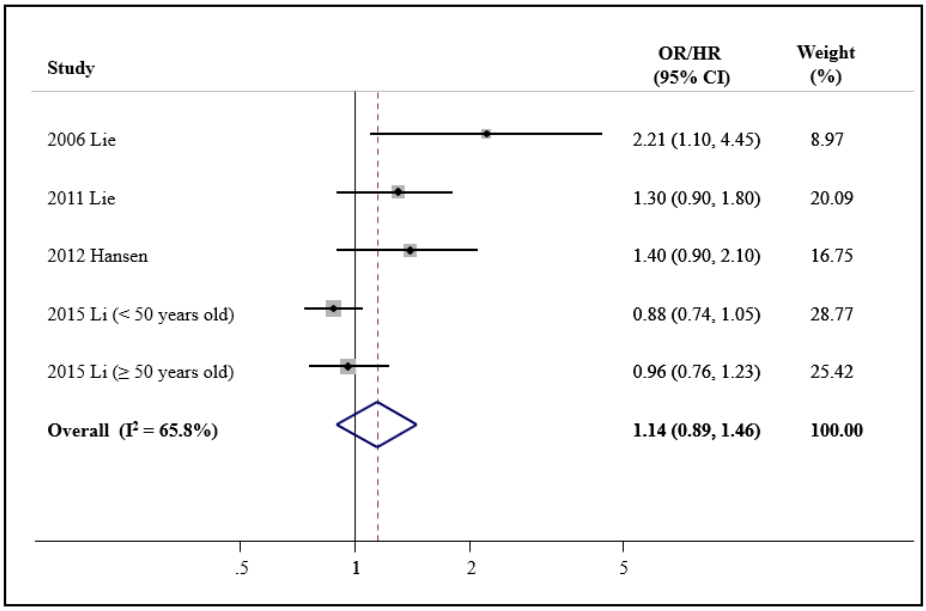

Figure 5. Association between night shift work and the risk of breast cancer in nested case-control studies (n = 4). OR, Odds Ratio; HR, Hazard Ratio; CI, Confidence Interval

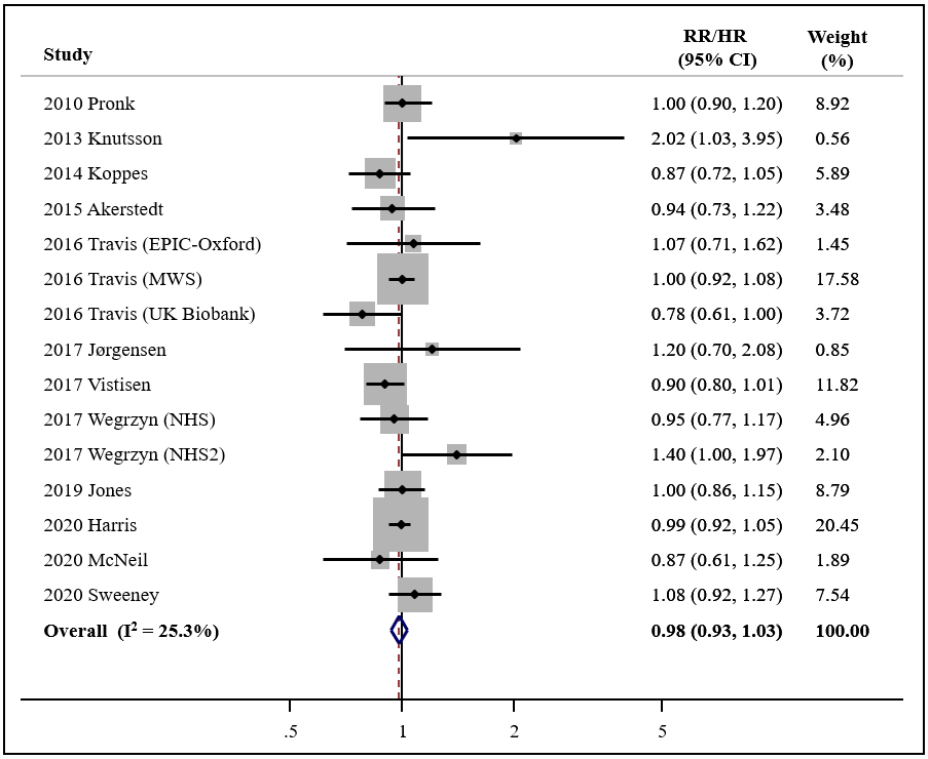

Figure 6. Association between night shift work and the risk of breast cancer in cohort studies (n = 15). RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

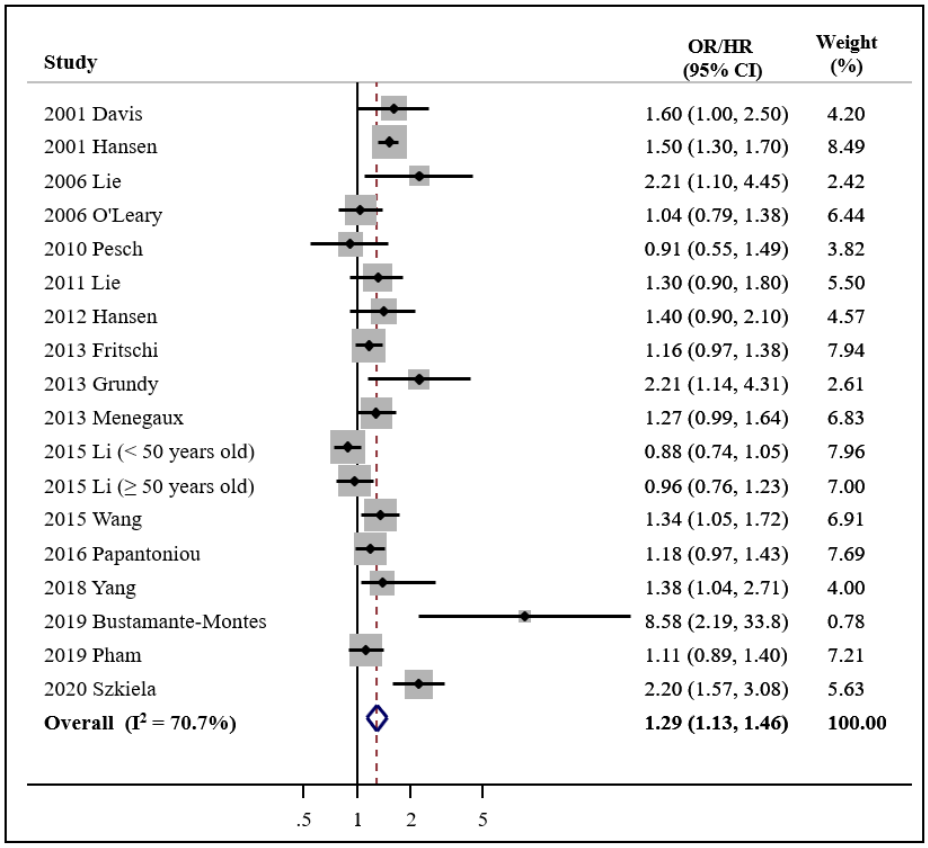

Figure 7. Association between night shift work and the risk of breast cancer in case-control studies and nested case-control studies (n = 17). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

3.5 Subgroup meta-analysis

3.5.1 Subgroup meta-analysis by shift schedule

In subgroup meta-analysis by shift schedule, both rotating and mixed shift work showed NSW was not associated with an increase in the risk of BC (OR/RR/HR, 1.33; 95% CI, 0.96 to 1.85; I^2 = 79.2%; n = 6, Figure 8 and OR/RR/HR, 1.05; 95% CI, 0.99 to 1.12; I^2 = 56.1%; n = 25, Figure 9, respectively). Only Hansen et al.′s study reported fixed shift work (OR, 1.5; 95% CI, 1.3 to 1.7) [81].

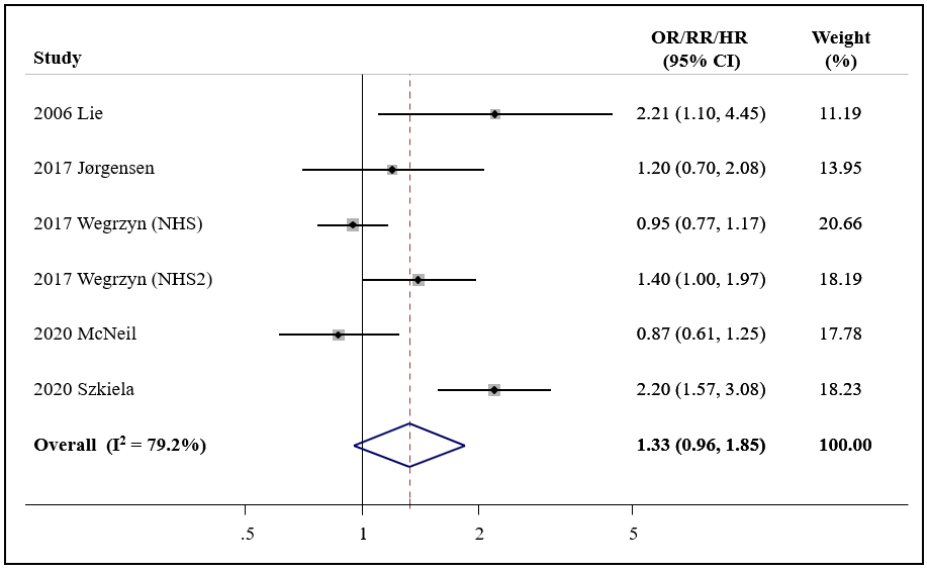

Figure 8. Subgroup meta-analysis by shift schedule: rotating shift (n = 6). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

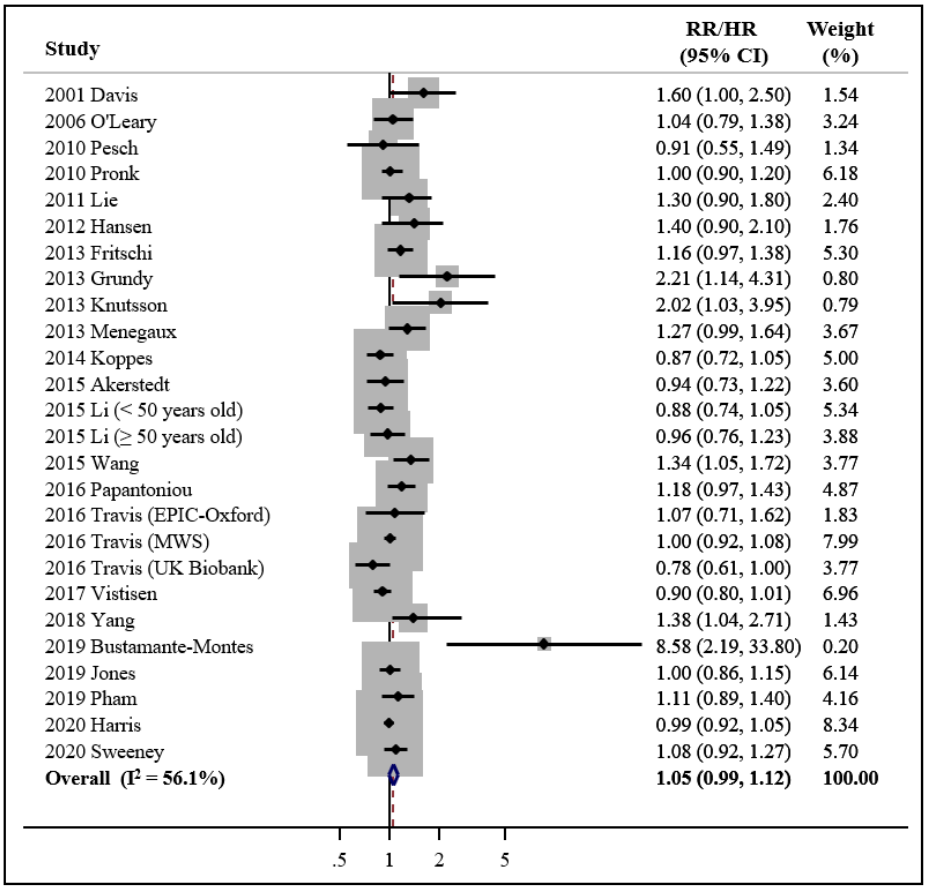

Figure 9. Subgroup meta-analysis by shift schedule: mixed shift (n = 25). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom

3.5.2 Subgroup meta-analysis by region

In subgroup meta-analysis by region, the increase in BC risk was found in the studies conducted in Europe (OR/RR/HR, 1.14; 95% CI, 1.01 to 1.29; I^2 = 79.9%; n = 17, Figure 10). Nevertheless, there was no significant association between NSW and the risk of BC in studies conducted in North America (OR/RR/HR, 1.13; 95% CI, 0.97 to 1.31; I^2 = 66.7%; n = 9, Figure 11), Asia (OR/RR/HR, 1.05; 95% CI, 0.92 to 1.19; I^2 = 49.0%; n = 5, Figure 12), and Australia (OR/RR/HR, 1.16; 95% CI, 0.97 to 1.38; n = 1).

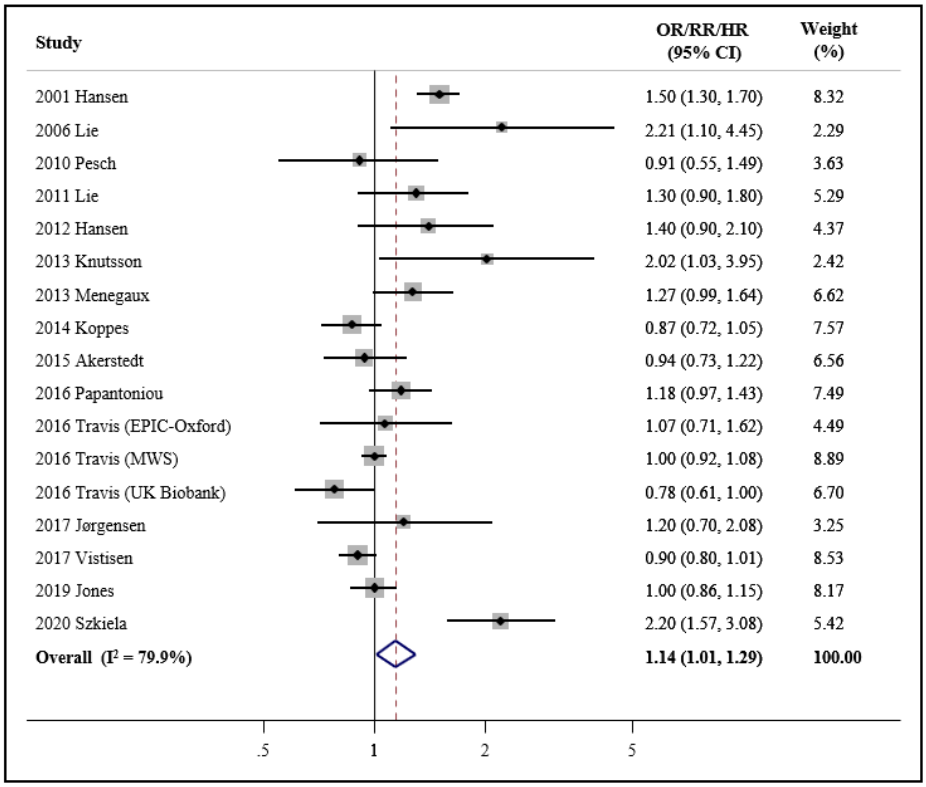

Figure 10. Subgroup meta-analysis by region: Europe (n = 17). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-

Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom

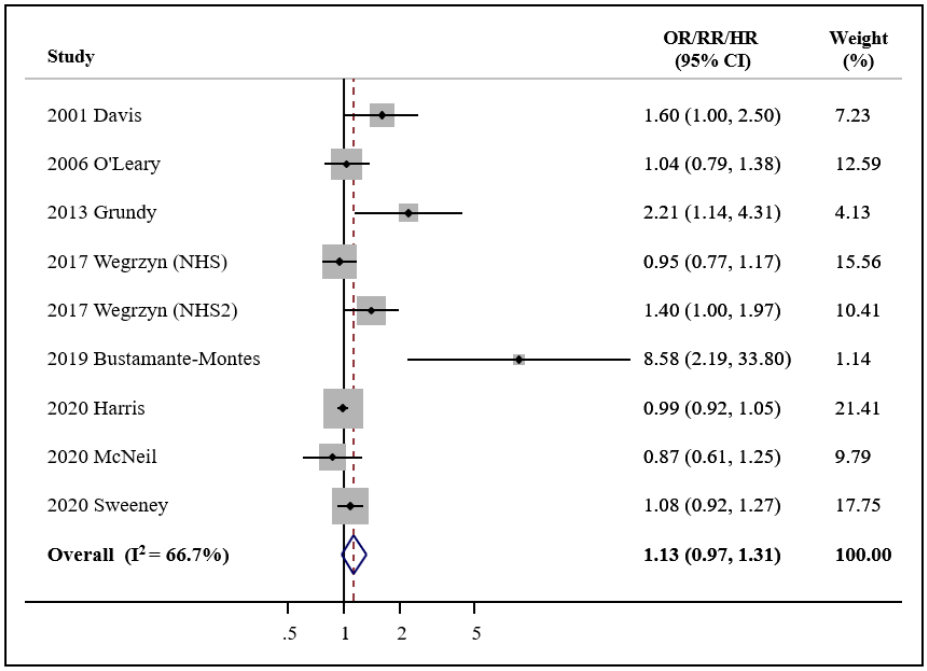

Figure 11. Subgroup meta-analysis by region: North America (n = 9). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

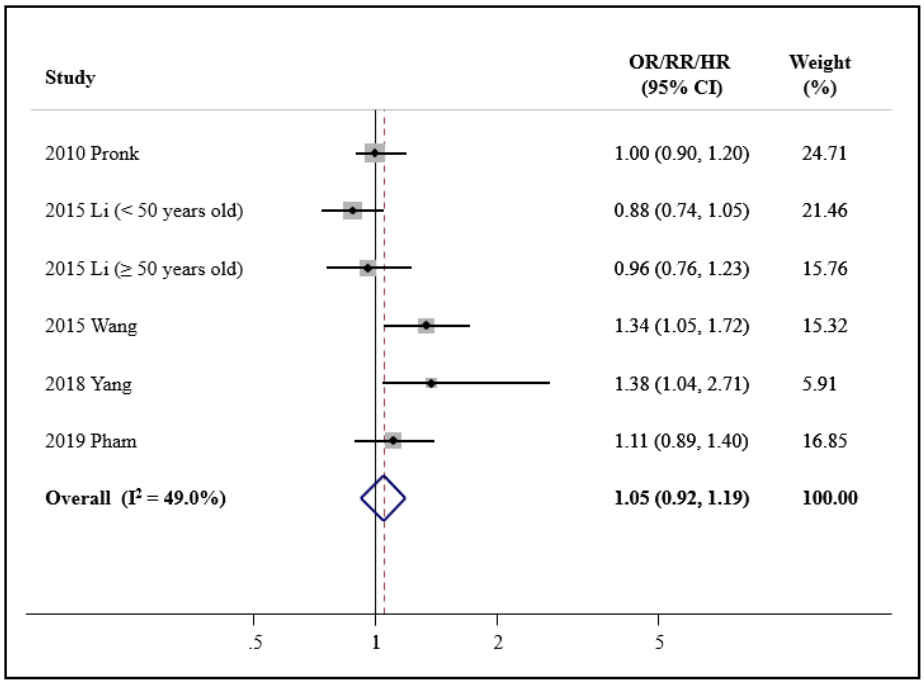

Figure 12. Subgroup meta-analysis by region: Asia (n = 5). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

3.5.3 Subgroup meta-analysis by occupation

In subgroup meta-analysis by occupation, NSW was not associated with the increased BC risk in women who worked as nurses (OR/RR/HR, 1.25; 95% CI, 0.98 to 1.59; I^2 = 52.1%; n = 5, Figure 13) or worked in industry (OR/RR/HR, 0.99; 95% CI, 0.80 to 1.22; I^2 = 49.5%; n = 2, Figure 14). In remaining studies, NSW increased 12% BC risk (OR/RR/HR, 1.12; 95% CI, 1.03 to 1.21; I^2 = 76.0%; n = 25, Figure 15).

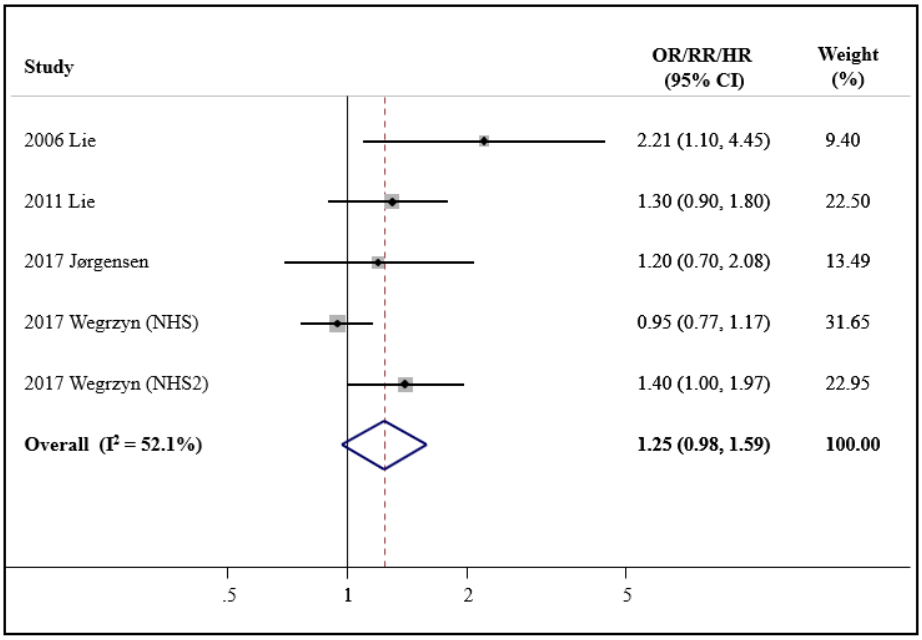

Figure 13. Subgroup meta-analysis by occupation: Nurse (n = 5). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

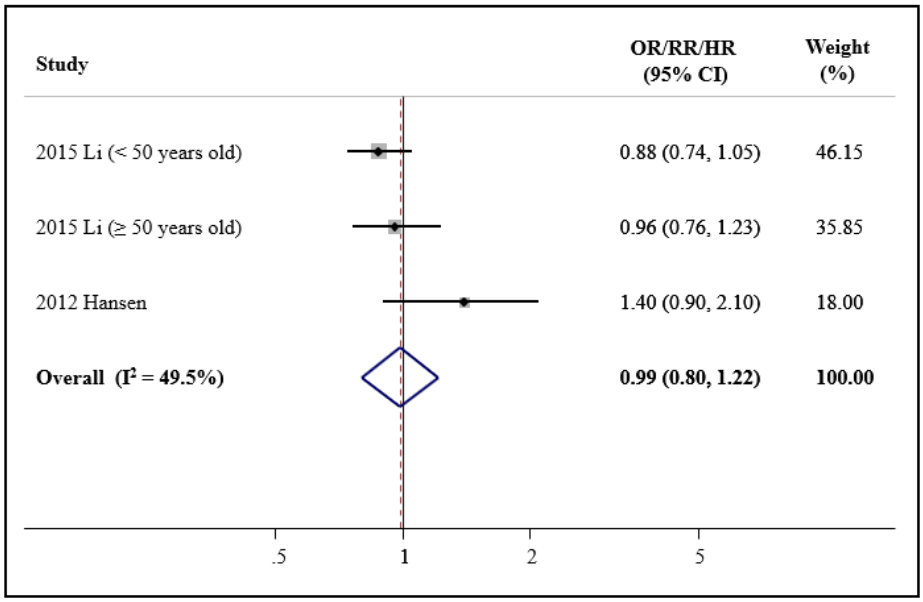

Figure 14. Subgroup meta-analysis by occupation: Industry (n = 2). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

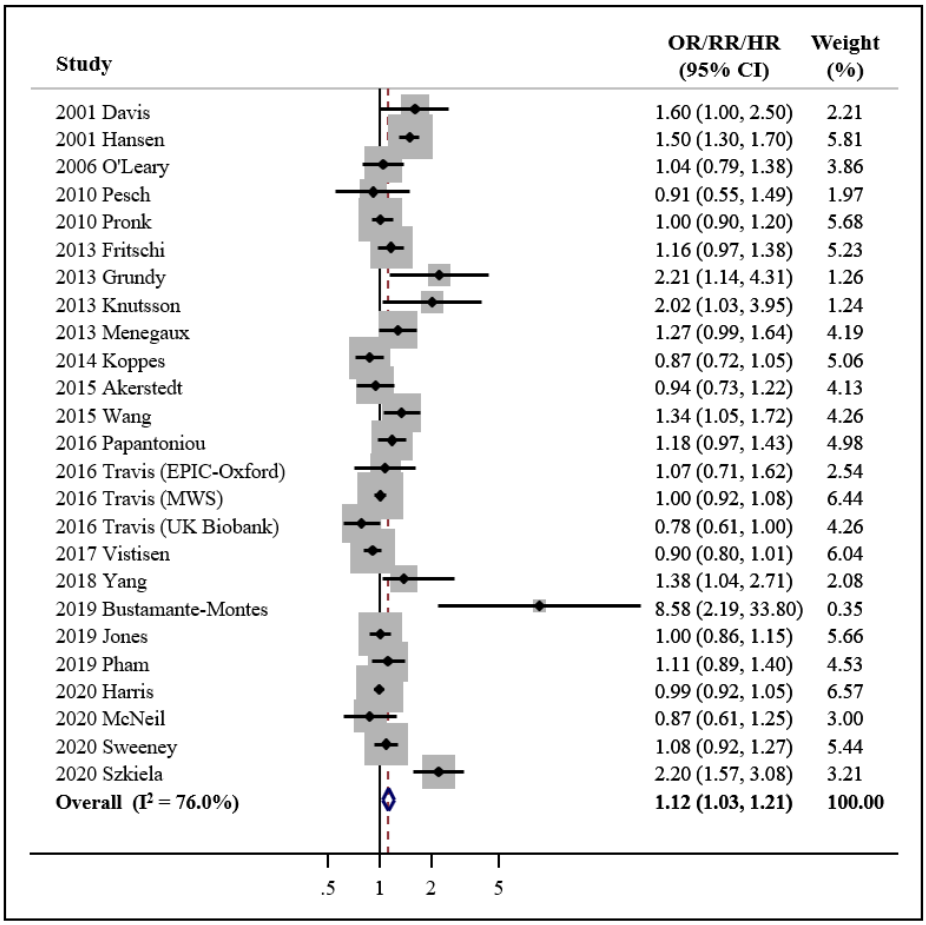

Figure 15. Subgroup meta-analysis by occupation: Other occupations (n = 25). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; MWS, Million Women Study; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; UK, United Kingdom

3.5.4 Subgroup meta-analysis by menopausal status

There were seven studies that reported the association between NSW and the risk of BC in subgroup meta-analysis by menopausal status. In both pre-menopausal women and post-menopausal women, no association between NSW and BC risk was found (OR/RR/HR, 1.16; 95% CI, 0.98 to 1.37; I^2 = 0.0%; n = 7, Figure 16 and OR/RR/HR, 1.12; 95% CI, 1.00 to 1.25; I^2 = 0.0%; n = 7, Figure 17).

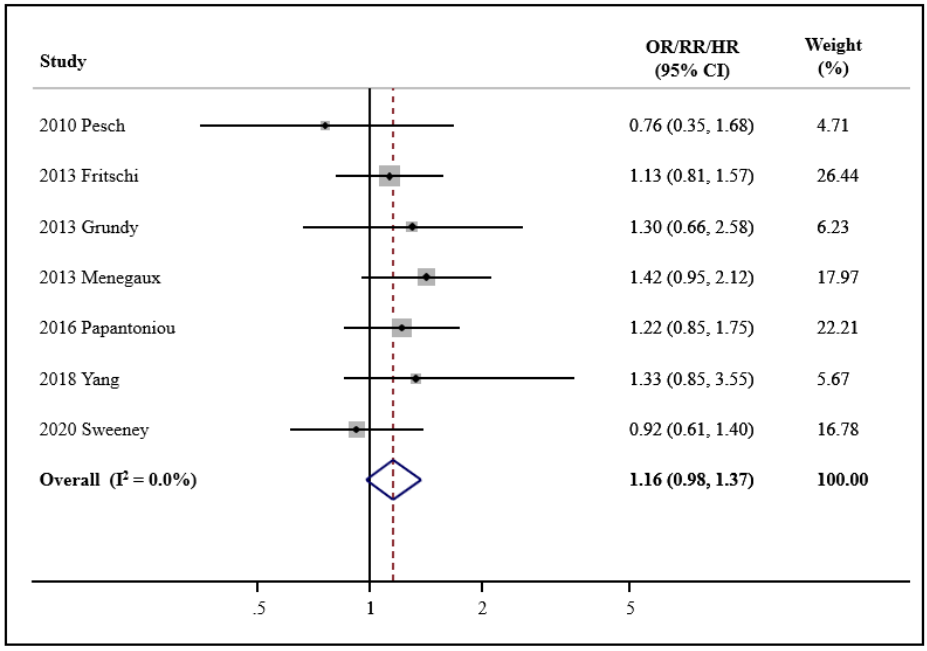

Figure 16. Subgroup meta-analysis by menopausal status: Pre-menopausal (n = 7). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

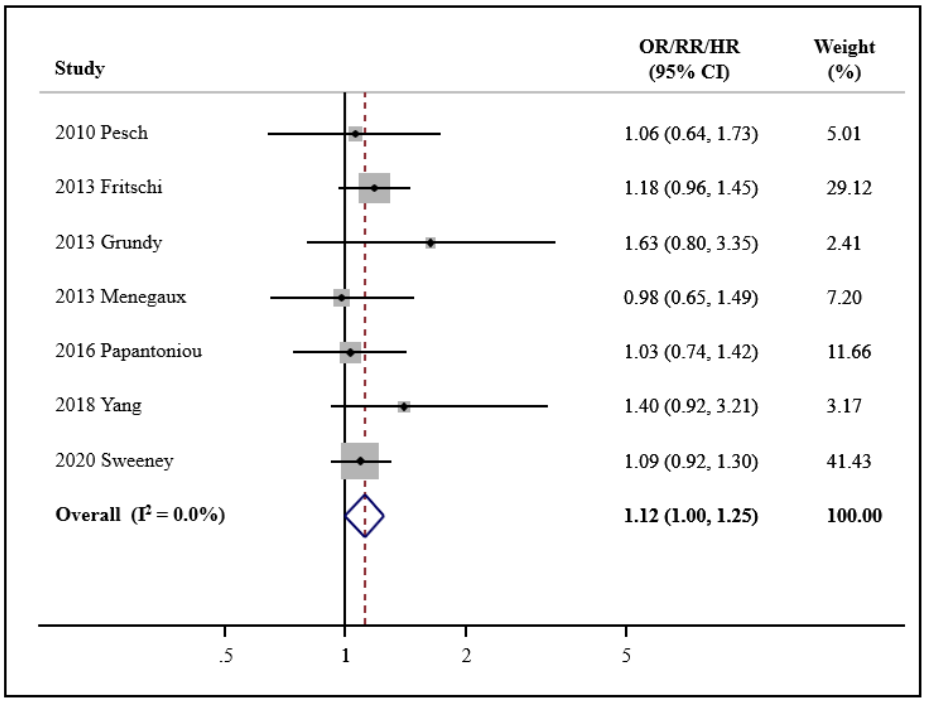

Figure 17. Subgroup meta-analysis by menopausal status: Post-menopausal (n = 7). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

3.5.5 Subgroup meta-analysis by follow-up rate or response rate

In the meta-analysis of eight studies that reported the follow-up rate in nested case-control studies and cohort studies or response rate in case-control studies more than 80%, there was no association between NSW and BC risk (OR/RR/HR, 1.09; 95% CI, 0.95 to 1.24; I^2 = 54.7%; n = 8, Figure 18). On the contrary, the risk of BC increased 17% in 24 remaining studies (OR/RR/HR, 1.12; 95% CI, 1.03 to 1.22; I^2 = 76.1%; n = 24, Figure 19).

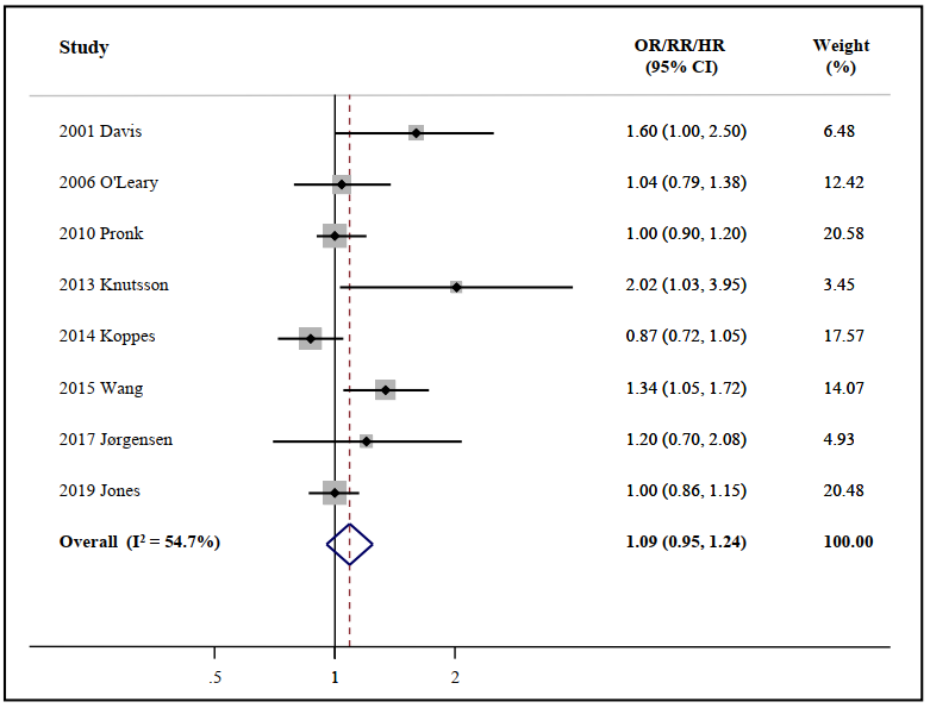

Figure 18. Subgroup meta-analysis by follow-up rate or response rate: more than 80% (n = 8). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

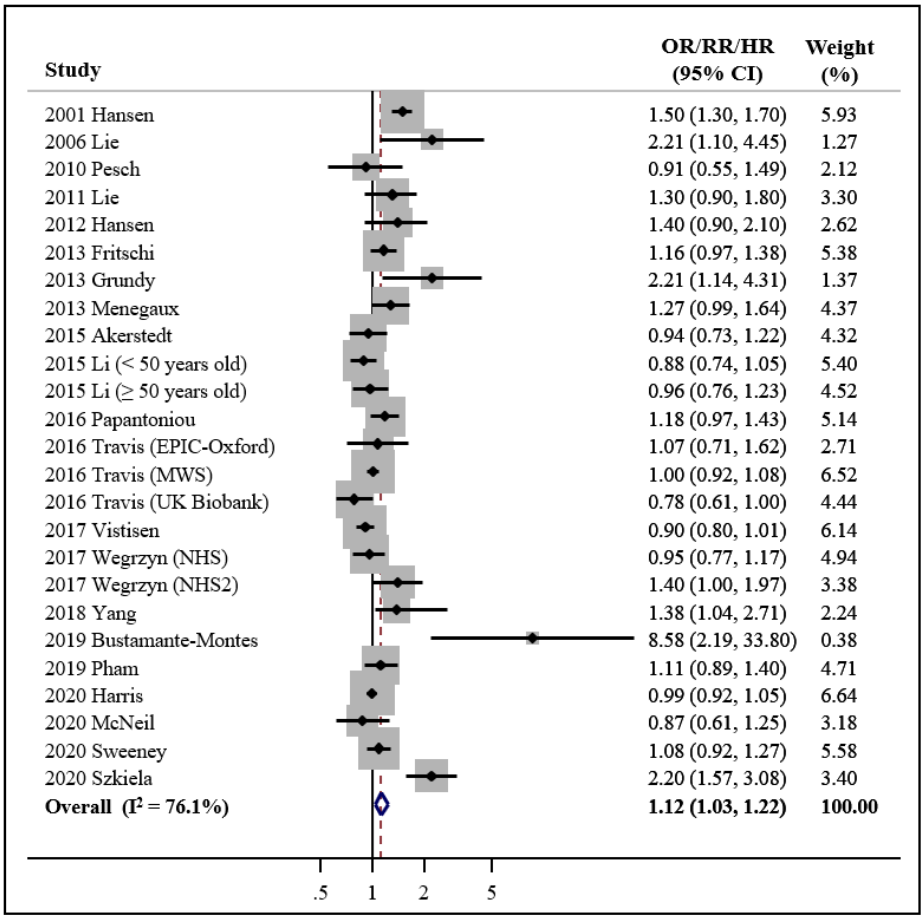

Figure 19. Subgroup meta-analysis by follow-up rate or response rate: less than 80% (n = 24). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

3.5.6 Subgroup meta-analysis by methodological quality

In the subgroup by methodological quality of studies, NSW was significantly associated with the increased BC risk in low-quality studies (OR/RR/HR, 1.17; 95% CI, 1.05 to 1.30; I^2 = 80.1%; n = 20, Figure 20). Conversely, no association between them was found in high-quality studies (OR/RR/HR, 1.05; 95% CI, 0.97 to 1.14; I^2 = 40.7%; n = 12, Figure 21).

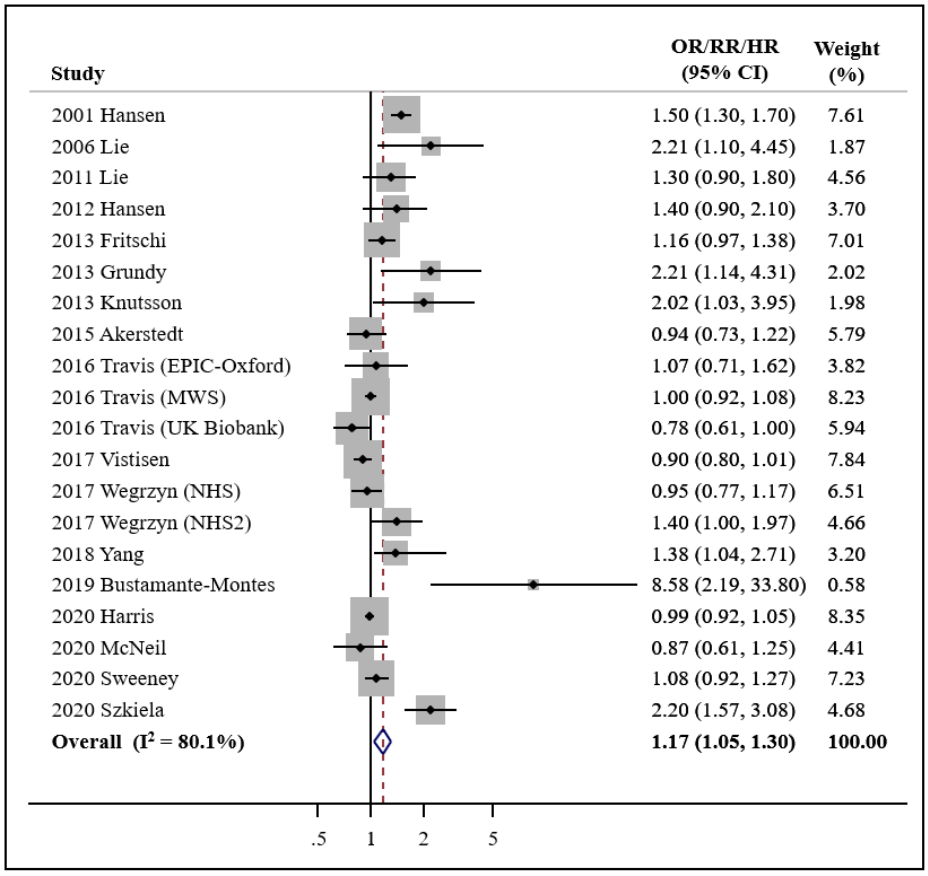

Figure 20. Subgroup meta-analysis by methodological quality: low quality (n = 20). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective

Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

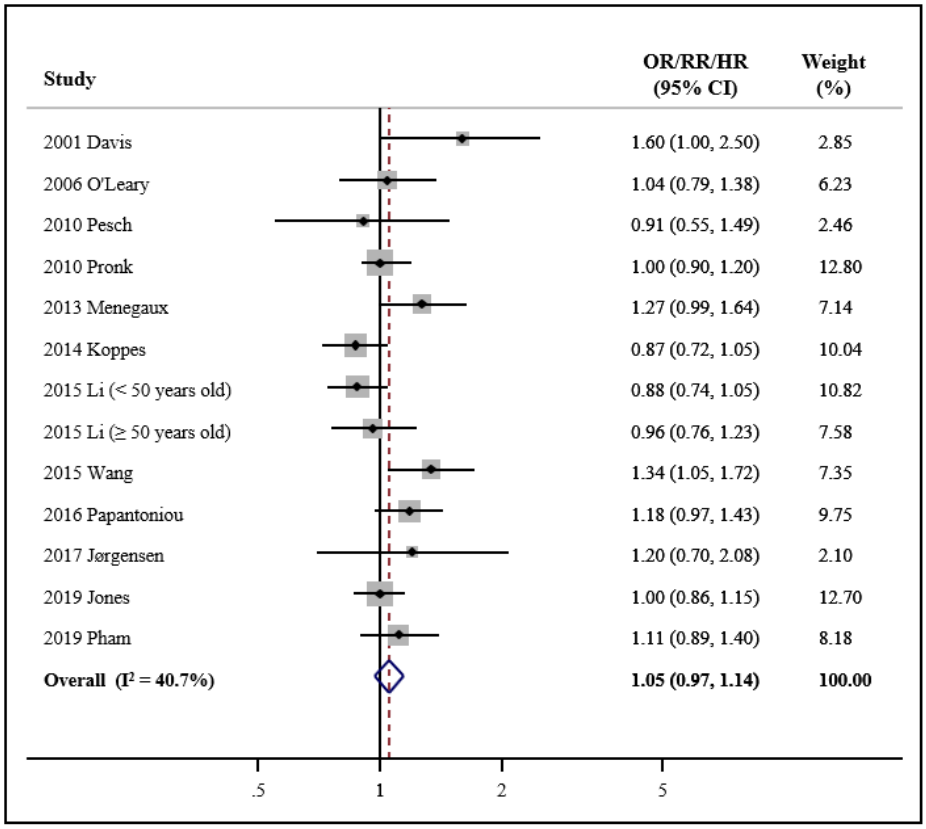

Figure 21. Subgroup meta-analysis by methodological quality: high quality (n = 12). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

3.5.7 Subgroup meta-analysis by duration of night shift work

The subgroup meta-analyses by duration of NSW indicated that there was no apparent association between NSW and the risk of BC in three subgroup: women working late less than 10 years (OR/RR/HR, 1.02; 95% CI, 0.98 to 1.05; I^2 = 2.0%; n = 18, Figure 22), women who worked in night shift from 10 to 20 years (OR/RR/HR, 0.99; 95% CI, 0.91 to 1.07; I^2 = 13.1%; n = 10, Figure 23), and even workers having night shift over 20 years (OR/RR/HR, 1.03; 95% CI, 0.95 to 1.11; I^2 = 36.6%; n = 14, Figure 24).

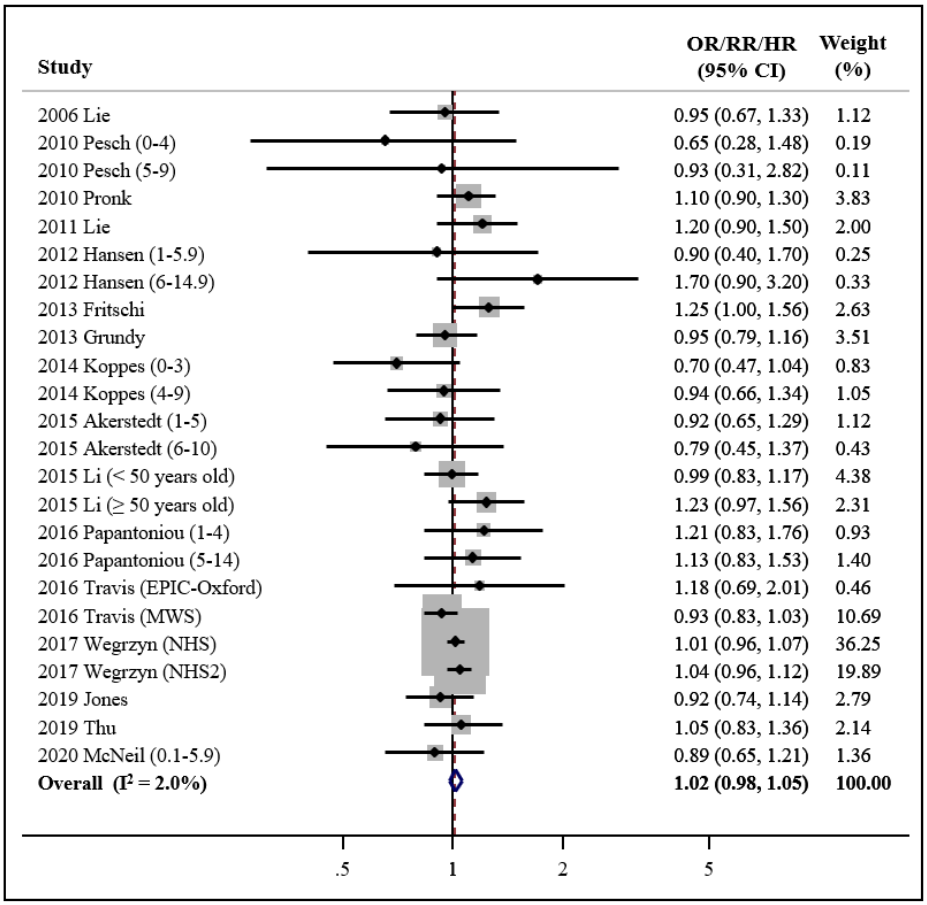

Figure 22. Subgroup meta-analysis by duration of night shift work: less than 10 years (n = 18). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; MWS, Million Women Study; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; NHS, Nurses' Health Study; NHS 2, Nurses' Health Study II

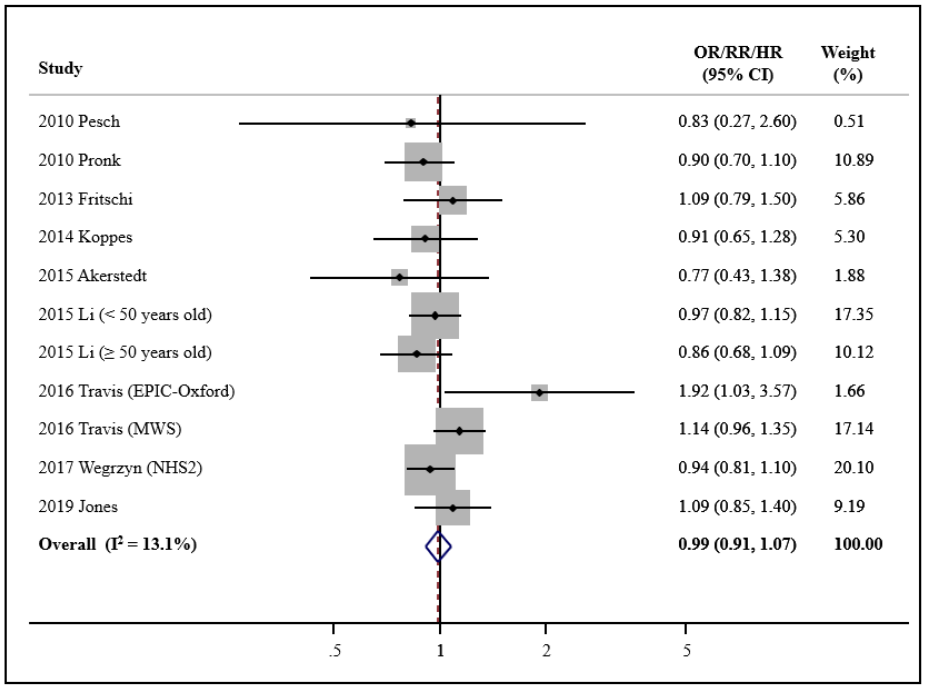

Figure 23. Subgroup meta-analysis by duration of night shift work: from 10 to 20 years (n = 10). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; NHS2, Nurses' Health Study II

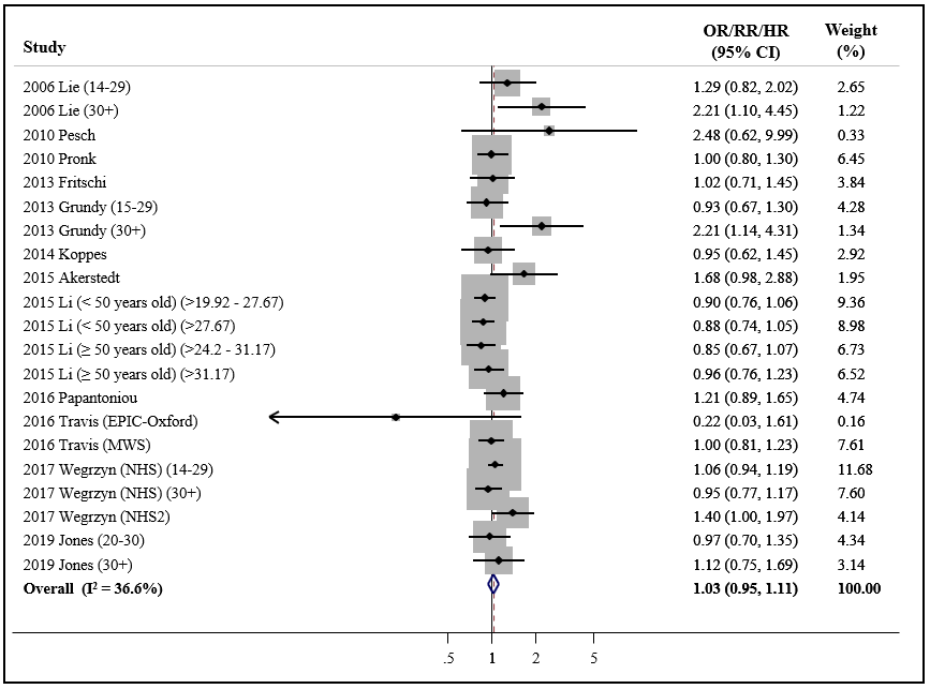

Figure 24. Subgroup meta-analysis by duration of night shift work: more than 20 years (n = 14). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval; MWS, Million Women Study; EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II

3.5.8 Subgroup meta-analysis by subtype of breast cancer

Figure 25 shows the findings in subgroup meta-analysis by subtypes of BC. In ER+ subtype, there was a significant association NSW and the risk of BC (OR/RR/HR, 1.25; 95% CI, 1.03 to 1.51; I^2 = 0.0%; n = 3). However, non-significantly increased OR/RR/HR were observed for the ER- (OR/RR/HR, 1.27; 95% CI, 0.89 to 1.80; I^2 = 9.0%; n = 3), ER+/PR+ (OR/RR/HR, 1.68; 95%

CI, 0.99 to 2.88; I^2 = 70.8%; n = 3), and ER+/PR- subtypes (OR/RR/HR, 1.36; 95% CI, 0.94 to 1.97; I^2 = 0.0%; n = 3).

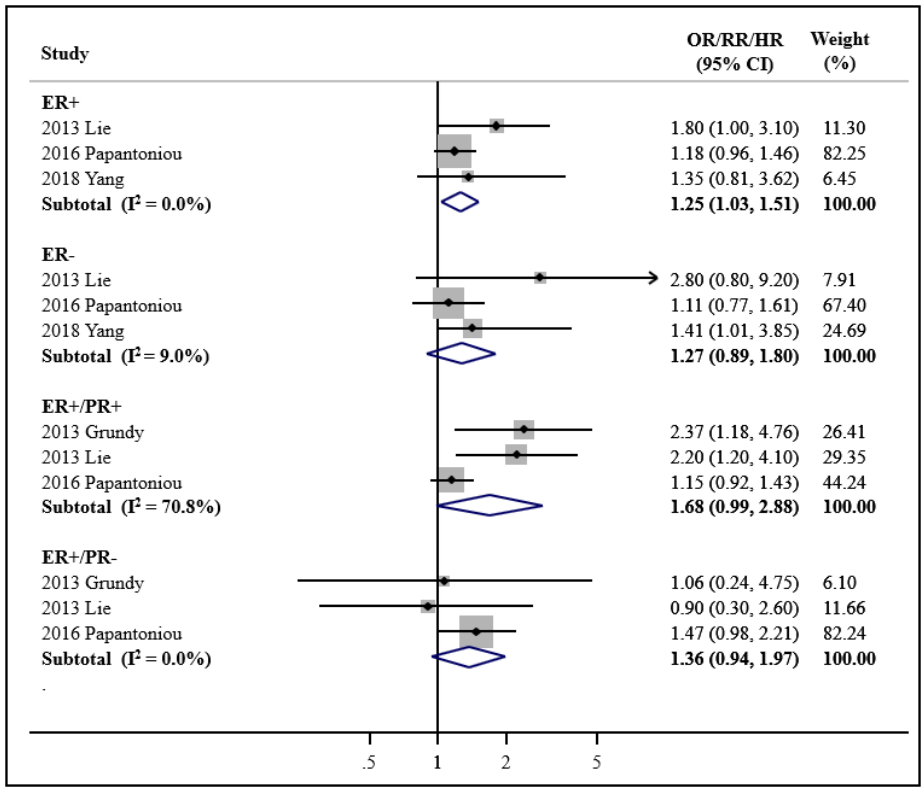

Figure 25. Subgroup meta-analysis by subtype of breast cancer. OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; CI, Confidence Interval

3.6 Subgroup meta-analysis by various factors

Table 5 shows the findings from the subgroup meta-analyses in each types of study (case-control study, nested case-control study, and cohort study) by various factors (shift schedule, region, occupation, follow-up rate or response

rate, methodological quality, and duration of night shift). Excluding the subgroup meta-analyses by duration of NSW, most subgroup meta-analyses of case-control studies showed the increased risk of BC in NSWers. In the subgroup meta-analyses of nested case-control studies, the increased BC risk by NSW was found in the rotating shift, in studies conducted in Europe, and low-quality studies. However, most subgroup meta-analyses of cohort studies showed no association between them.

Table 5. Association between night shift work and breast cancer risk in subgroup meta-analysis by various factors.

Factors	Case-control study		Nested case-control study		Cohort study	
	No. of study	OR (95% CI)	No. of study	OR/HR (95% CI)	No. of study	RR/HR (95% CI)
Shift schedule						
Fixed	1	1.50 (1.30-1.70)	0	-	0	-
Rotating	1	2.20 (1.57-3.08)	1	2.21 (1.10-4.45)	4	1.05 (0.85-1.30)
Mixed	11	1.24 (1.09-1.39)	3	1.05 (0.85-1.29)	11	0.97 (0.93-1.03)
Region						
Europe	5	1.38 (1.12-1.70)	3	1.43 (1.11-1.83)	9	0.95 (0.88-1.03)
North America	4	1.83 (1.03-3.26)	0	-	5	1.02 (0.93-1.11)
Asia	3	1.23 (1.05-1.44)	1	0.91 (0.79-1.04)	1	1.00 (0.87-1.15)
Australia	1	1.16 (0.97-1.38)	0	-	0	-
Occupation						
Industry	13	1.34 (1.17-1.53)	2	0.99 (0.80-1.22)	0	-
Nurses	0	-	2	1.55 (0.95-2.53)	3	1.13 (0.86-1.47)
Others*	0	-	0	-	12	0.97 (0.93-1.02)

Follow-up rate or response rate						
≥ 80%	3	1.26 (1.01-1.57)	0	-	5	1.00 (0.88-1.14)
< 80%	10	1.37 (1.16-1.61)	4	1.14 (0.89-1.46)	10	0.98 (0.92-1.03)
Methodological quality						
High (8 or 9 stars)	7	1.19 (1.08-1.32)	1	0.91 (0.79-1.04)	4	0.97 (0.89-1.06)
Low (6 or 7 stars)	6	1.65 (1.27-2.15)	3	1.43 (1.11-1.83)	11	0.98 (0.92-1.05)
Duration of night shift work (years)						
Never		Ref.		Ref.		Ref.
> 0-10	5	1.07 (0.96-1.20)	4	1.09 (0.97-1.24)	9	1.00 (0.96-1.04)
> 10-20	2	1.07 (0.78-1.45)	1	0.93 (0.81-1.07)	7	1.01 (0.90-1.15)
> 20	4	1.18 (0.91-1.54)	2	0.95 (0.83-1.10)	8	1.05 (0.96-1.14)

* Others include non-classified occupational studies and classified occupational studies, but don't include nurses and women who work on factories. OR, Odds ratio; RR, relative risk; HR, hazard ratio; CI, confident interval.

3.7 Publication bias

Figure 26 and Figure 27 show that there is publication bias when all the studies or only nested case-control studies were included in the meta-analysis (Begg's funnel plots were asymmetric; Egger's test: p for bias = 0.005 and 0.001, respectively). However, no publication bias was observed in case-controls studies and cohort studies (Egger's test: p for bias = 0.309 and 0.495, Figure 28 and Figure 29, respectively).

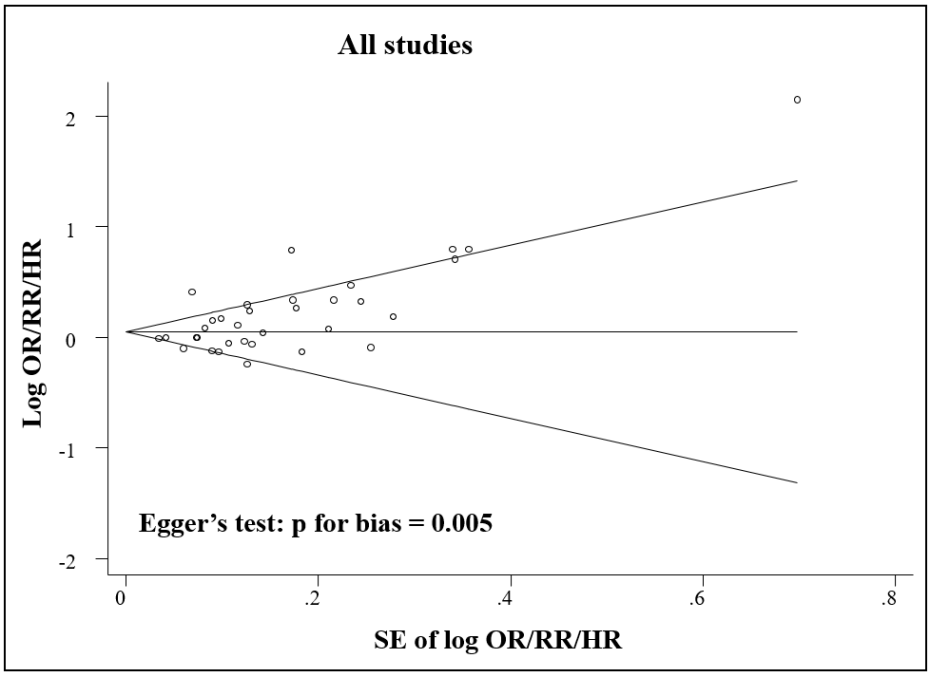

Figure 26. Begg's funnel plot and Egger's test to identify publication bias in a meta-analysis of all studies (n = 32). OR, Odds Ratio; RR, Relative Risk; HR, Hazard Ratio; SE, Standard error

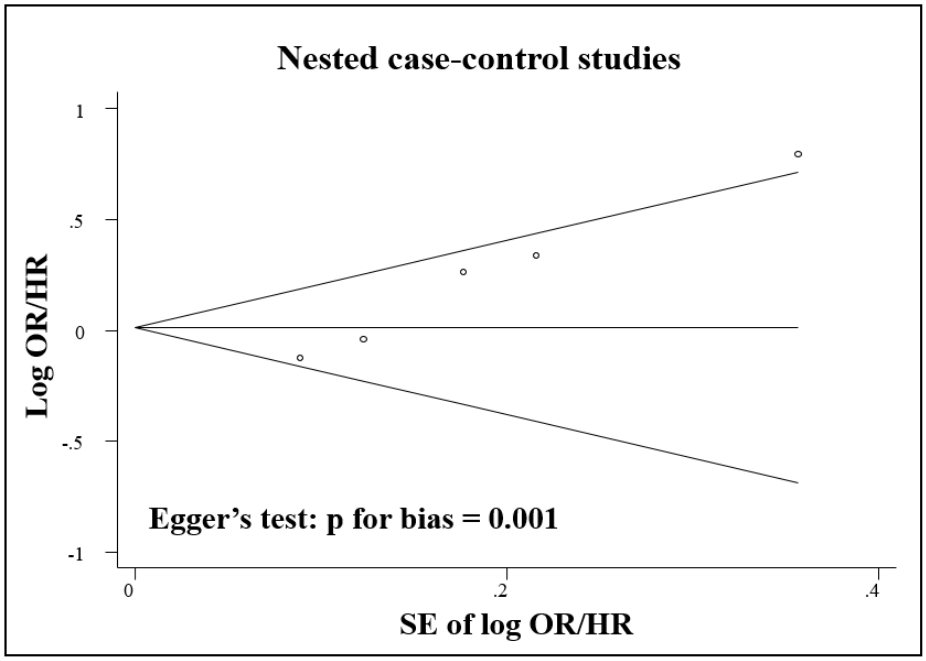

Figure 27. Begg's funnel plot and Egger's test to identify publication bias in a meta-analysis of nested case-control studies (n = 4). OR, Odds Ratio; HR, Hazard ratio; SE, Standard error

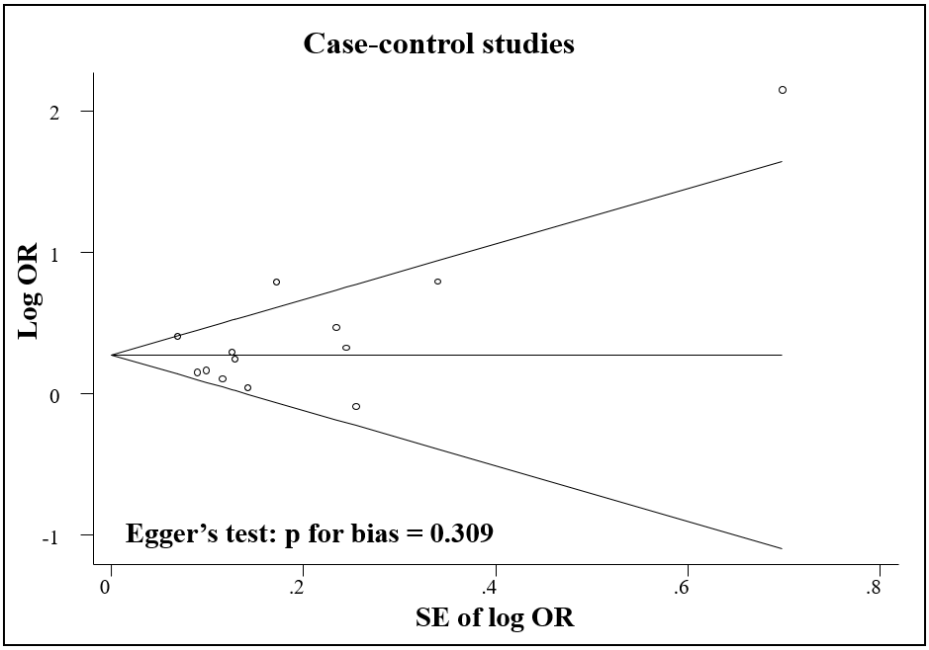

Figure 28. Begg's funnel plot and Egger's test to identify publication bias in a meta-analysis of case-control studies (n = 13). OR, Odds Ratio; SE, Standard error

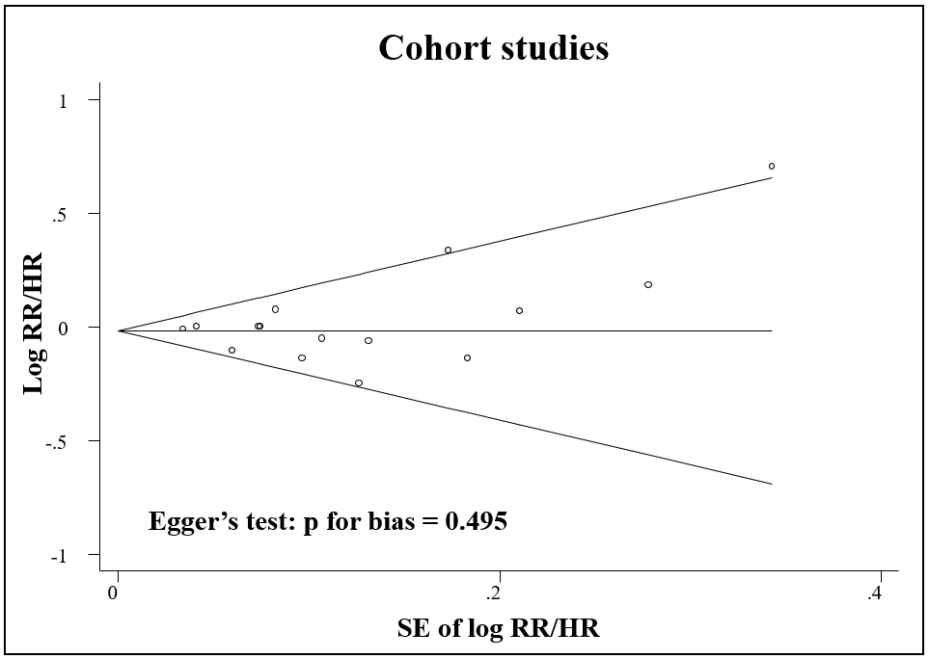

Figure 29. Begg's funnel plot and Egger's test to identify publication bias in a meta-analysis of cohort studies (n = 15). RR, Relative Risk; HR, Hazard ratio; SE, Standard error

3.8 Dose-response analysis

Due to the lack of the numbers of the population at risk in cohort studies, we only calculated the dose-response relationship in case-control studies. Figure 30 showed the curve representing dose-response relationship between NSW and BC risk in case-control studies. We estimated the linearity relationship using a two-stage random effect model ($p < 0.001$). For every 5 and 10 years of NSW, the risk of BC increase by 3.7% and 7.6% (OR, 1.037; 95% CI, 1.011 to 1.064

and OR, 1.076; 95% CI, 1.023 to 1.132, respectively).

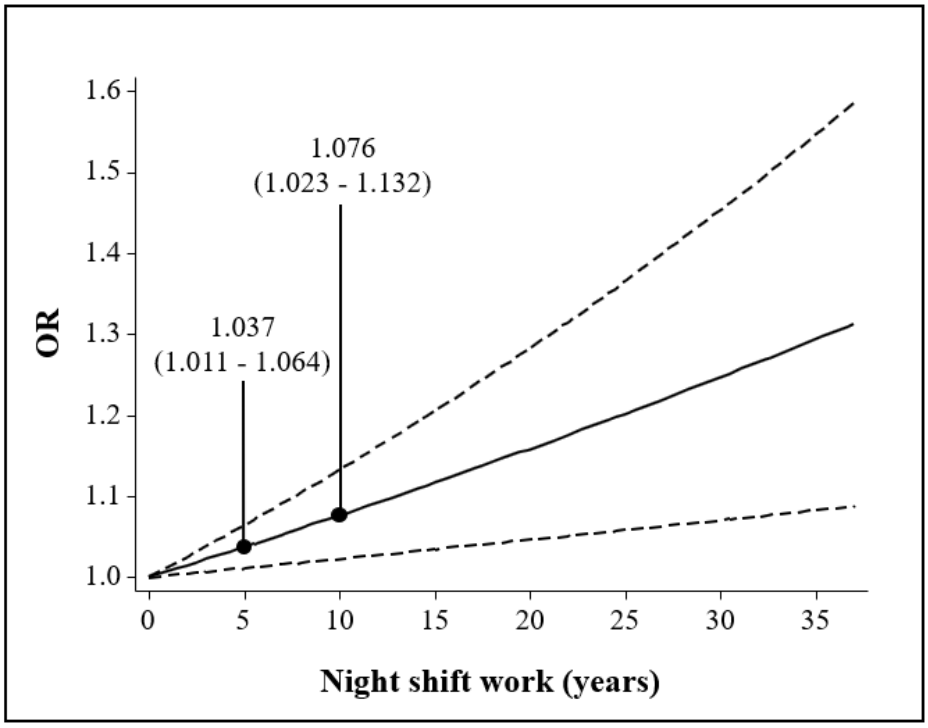

Figure 30. Dose-response relationship between night shift work and breast cancer risk. The middle line of the curves represents the pooled effect and the upper and lower side lines represent 95% CI of the pooled effect. OR, odds ratio

4. Discussion

4.1 Summary of the findings

In the meta-analysis of 32 observational epidemiological studies, even though NSW increased the risk of BC in all studies and case-control studies, there was no significant association between them in both nested case-control studies and cohort studies. Also, their association was not found in people working late for more than 20 years, compared with women who never have night shift.

4.2 Assessment of bias

The discrepancy in the findings on the association between NSW and the risk of BC between case-control studies and nested case-control studies or cohort studies might be due to selection bias and recall bias. Normally, case-control studies have a higher risk of selection bias and recall bias than cohort studies. First, selection bias occurs when case or control groups are non-randomly selected from the population. The low response fractions might be one of the possible reasons for selection bias [23]. Also, the recruitment of cases from the population-based BC registry and controls from screening clinics might lead to selection bias [11]. Because some BC cases might not participate in screening, they might have been to be included as controls [11]. Further,

because NSWers often sleep in daytime and could not answer the phone call from researchers, a sampling bias, which is one of the selection biases, can occur [28]. Also, recall bias can occur because participants in cases might be more sensitive and reported exposure more readily than in controls [13]. This might overestimate the sleep behaviors [11,13,33]. These important biases might be associated with the findings of the increased BC risk by NSW in case-control studies. Prospective cohort studies are less vulnerable to these biases in general. Thus, given that cohort studies provide higher evidence than case-control studies, the findings that there is no association between them in cohort studies are more reliable.

4.3 Possible mechanisms

Regarding the increased risk of BC by NSW, its potential biological mechanisms remain unclear. According to previous studies, the reduction of melatonin and the dysfunction of circadian genes might be a possible reason for the increased risk of BC by NSW [83, 84, 110].

Melatonin acts as an anti-cancer agent through two pathways: receptor dependent or independent mechanism [113]. In the first pathway, melatonin binds to Gi-protein-coupled plasma membrane receptors to transform inactive Gi protein to active form that inhibits adenylate cyclase [113]. As a result, tumor formation was inhibited by attenuation in adenylate cyclase-dependent

hallmarks of cancer such as anti-estrogenic properties, reduction of cell proliferation, prevention of invasiveness, and pro-differentiation [113]. In the receptor independent mechanism, melatonin fights cancer through the following five activities: decreasing telomerase activities in cancer cells, inhibiting angiogenesis, exerting anti-oxidant activities, activating PPAR/RXR and leading to apoptosis on tumor cells, and enhancing the immune system against cancer during treatment [113, 114]. Melatonin is mainly produced and released by the pineal gland during the night and regulated by the light-dark cycle. Thus, the change in the time point of light exposure disorders the synthesis of melatonin [115]. The reduction of melatonin levels was reported among NSWers [116, 117]. However, these mechanisms have been suggested mainly from the findings from laboratory studies and animal studies.

The roles of circadian genes in cancer, especially in BC have been studied for many years. However, complicated mechanisms of circadian genes in tumor development have not been explored clearly. So far, the main clock genes have been identified include Period1/2/3 (Per1/2/3), Casein kinase 1δ/ε (CK1δ/ε), Circadian locomotor output cycles kaput k (Clock), Brain and muscle Aarnt-like protein 1 (BMAL1), Differentiated embryo-chondrocyte expressed gene 1/2 (Dec1/2), Cryptochrome1/2 (Cry1/2), Neuronal PAS domain protein 2 (NPAS2), nuclear receptor subfamilies (NR1D), and retinoid-related orphan receptors (Rors) [118]. At the cell level, clock genes active based on positive and negative transcription-translation autoregulatory feedback loops in a cycle

of about 24 hours, therefore, make circadian rhythms. [119]. In addition, clock genes regulate some genes that play crucial roles in the cell cycle and cell division [120]. Their aberrantly expressed might break the cell cycle [120]. Moreover, many clock proteins that are under the control of the circadian rhythm closely related to repair lesion of DNA in the cell cycle [119]. In addition, many genes that regulated cell proliferation, invasion, apoptosis, angiogenesis, and metastasis were suggested to have periodic expressions over a 24-hour cycle [120]. These genes might be controlled by circadian clock genes [120]. In summary, the abnormal expressions of circadian clock genes lead to tumorigenesis and tumor progression.

An overexpression of CLOC, BMAL1, PER1, PER2, NPAS2, and NR1D and a lower expression of PER3, CRY1, and CRY2 were found in nurses having night shift [121]. Hypermethylation and hypomethylation in the promoter region of clock genes change levels of gene expression [122]. In some studies, hypermethylation of CRY2 and hypomethylation of CLOCK in NSWers were shown [123]. In another study, an increase in methylation levels of the CLOCK, BMAL1, and CRY1 genes were observed in BC cases who engaged in night shifts [124]. Epidemiological studies gave inconsistent findings in this relationship. The mechanisms contributing to cancer by circadian genes have been not understood fully at the molecular level.

4.4 Comparisons with previous studies

Meanwhile, previous meta-analyses of epidemiological studies have reported inconsistent findings on this topic. The findings of the published meta-analyses were summarized in Table 6 [64, 88, 89, 125-129]. All the meta-analyses including only case-control studies resulted in the increased risk of BC by NSW. However, all the meta-analyses including only cohort studies showed no statistically significant association between them. In addition, most of the previous meta-analyses of observational studies reported that there was no increase in BC risk in long term NSWers. These findings are consistent with ours.

Table 6. Previous meta-analyses of observational epidemiological studies and systematic reviews on the association between night shift work and breast cancer risk.

Study	Number of included studies				Comparisons	OR/RR/HR (95% CI)	Conclusion
	Total	Case-control study	Nested case-control study	Cohort study			
2005 Megdal [125]	6	1	1	4	Never vs. ever	1.51 (1.36-1.68)	NSW increases BC risk
2013 Kamdar [126]	8	5		3	Never vs. ever	1.21 (0.99-1.47)	No association between NSW and BC risk
					Never vs. < 8 ys	1.13 (0.97-1.32)	
					Never vs. ≥ 8 ys	1.04 (0.92-1.18)	
2013 Wang [127]	10	4	3	3	Never vs. ever	1.19 (1.05-1.35)	NSW increases BC risk
		4	3		Never vs. ever	1.06 (1.02-1.09)	
				3	Never vs. ever	1.02 (1.00-1.04)	
2013 Ijaz [128]	12	9			Never vs. ever	1.09 (1.02-1.20)	No association between NSW and BC risk
				3	Never vs. ever	1.01 (0.97-1.05)	
2013 Jia [129]	13	8		5	Never vs. ever	1.20 (1.08-1.33)	NSW increases BC risk
		8			Never vs. ever	1.32 (1.17-1.50)	
				5	Never vs. ever	1.08 (0.97-1.21)	
					Never vs. ≥ 15 ys	1.15 (1.03-1.29)	

2015 He [89]	15	11	4	Never vs. ever	1.19 (1.08-1.32)	NSW increases BC risk
2016 Travis [64]	10		10	Never vs. ever Never vs. ≥ 20 ys Never vs. ≥ 30 ys	0.99 (0.95-1.03) 1.01 (0.93-1.10) 1.00 (0.87-1.14)	NSW has little or no effect on BC risk
2018 Cordina-Duverger [88]	5	5		Never vs. ever Never vs. < 10 ys Never vs. 10-19 ys Never vs. ≥ 20 ys	1.12 (1.00-1.25) 1.18 (1.03-1.36) 0.98 (0.78-1.22) 1.10 (0.87-1.39)	NSW increases BC risk in pre-menopausal women, but not in post-menopausal women.

Abbreviations: OR, odds ratio, RR, relative risk; CI, confident interval; NSW, Night shift work; BC, Breast cancer. OR. Odds ratio; RR, relative risk; HR, hazard ratio; CI, confident interval; ys, years.

4.5 Strengths and limitations

To the best of our knowledge, the current study is the most comprehensive meta-analysis of observational epidemiological studies on the association between NSW and the risk of BC. Our meta-analysis encompassed a large number of individual studies, especially cohort studies with a wide range of populations and a set of data collected in long periods.

Our study has several limitations. First, the definition of NSW varied not only from country to country, but also in each study. The differences in definitions of NSW between countries are shown in Table 1. Also, Pronk et al. [63] defined night shift as working after 22:00 at least 3 times per month for over 1 year, while working at night shifts regularly between 21:00-08:00 for at least 2 months was regarded in Pham et al.'s study [12]. This ambiguous definition might lead to misclassification and changes of the pooled effect sizes. Second, most studies ascertained exposures based on the self-report of the participants, which could lead to recall bias and misclassification bias [56, 83, 98, 112]. Besides, not all studies classified the types of night work (fixed, rotating, and mixed) and adjusted confounders, which might lead to these biases [82, 84, 111]. Third, due to the lack of data in cohort studies, we only evaluated the dose-response relationship between NSW and BC risk in case-control studies, instead of all studies. The linear dose-response relationship in this analysis was similar to the results of the meta-analysis of case-control studies.

In addition, insufficient data in subtypes of BC make the meta-analysis in this subgroup less comprehensive. Lastly, most of the studies included in this meta-analysis did not consider some important confounding factors such as sleep quality, exposure to light at night, or chronotype [56, 109, 110], which are closely related to circadian disruption and suppression of melatonin and ultimately might lead to the development of BC [114, 130].

5. Conclusion

In this meta-analysis of 32 observational studies, NSW increased the risk of BC in all studies and case-control studies. However, no significant association between them was found in both nested case-control studies and cohort studies. Also, there was no association between NSW for over 20 years and BC risk. Given that cohort studies provide higher evidence than case-control studies, there is no significant association between NSW and the risk of BC. Further large prospective cohort studies are warranted to confirm these associations. Despite the null results, the current study may be helpful to other investigators and policy makers.

APPENDIX

A. PRISMA Checklist

Section/Topic	#	Checklist item	Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structure summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-9
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	10
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide	11

		registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	13
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	12
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	13
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	14
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	14
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	14

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	14-15
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	15
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	15-16
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	16
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	16
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	17-18
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and	18-30

		provide the citations.	
Risk of bias within individual studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	31
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	31
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	30-37
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	59-62
Additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	38-58, 62-63
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	64
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	71-72

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	73
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

B. PROSPERO Registration Certificate

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Night shift work and risk of breast cancer: meta-analysis of case-control, cohort and nested case-control studies

Nhung Van, Quy Luu, Seung-Kwon Myung

Citation

Nhung Van, Quy Luu, Seung-Kwon Myung. Night shift work and risk of breast cancer: meta-analysis of case-control, cohort and nested case-control studies. PROSPERO 2020 CRD42020147114 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020147114

Review question

Objective: Associations between night shift work and risk of breast cancer.

Outcome: odds ratio of case-control, cohort and nested case-control studies and all of them. Compare the odds ratio of each type of studies.

Population: female population

Exposure: night shift work

Comparator: daytime work

Outcome: breast cancer risk

Searches

Date: 10th September 2019

Language: Not limited

Database: PubMed and Embase

Use predetermine keywords related to night shift work and breast cancer limited humans.

Types of study to be included

Case-control, Cohort and Nested Case-control Studies

Condition or domain being studied

Breast cancer in women with night shift work.

Participants/population

Inclusion: adult women

Exclusion: In cohort and nested case-control studies, women who diagnosed with breast cancer prior to follow-up were not included.

Intervention(s), exposure(s)

Exposure: night shift work. Night shift work is defined as a working schedule that involved partly or entirely working from 00:00 to 6:00 a.m. and more than 3 hours, at least 3 nights per month. This definition includes overnight, late evening (end after 00:00) and early morning (start before 6:00) shifts.

Comparator(s)/control

Case-control study: participants in the control group were people who did not contract breast cancer and matched some characteristics (such as age, area, occupation, etc.) of participants in the case group.

Cohort study: women who had daytime work.

Nested case-control study: In the cohort population, when a breast cancer case was identified, then a control of that case was included.

Main outcome(s)

Main outcome: breast cancer risk in women.

* Measures of effect

Measurement: based on the data of each individual study, we calculated the pooled odds ratio of case-control and nested case-control studies, the pooled relative risk from cohort studies with their 95% confidence intervals estimated in a random-effect model.

Additional outcome(s)

None

* Measures of effect

None

Data extraction (selection and coding)

Data extraction: first author, publication year, study location, study design, number of cases, participant's sex, occupation, schedule of night shift work, the definition of exposure, adjusted OR with 95% CI, adjusted covariates, exposure assessment, quality score. ORs of the shortest and longest exposure time were extracted from articles as the exposure indicator for statistical analysis.

Researcher: Nhung Van and Quy Luu independently search eligible articles. Discrepancies are solved by Professor Myung.

Risk of bias (quality) assessment

We used the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation) to assess confidence in effect estimates. The GRADE system classifies the quality of evidence in one of four levels: high, moderate, low, and very low.

High quality - Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality - Any estimate of effect is very uncertain.

We also examined publication bias regarding the studies included in the final analysis by using Begg's funnel plot and Egger's test. If the publication has any bias, the Begg's funnel plot is asymmetrical or the P-

value is found to less than 0.05 by Egger's test. We used the Stata SE version 14 software package (StataCorp, College Station, Texas, USA) for statistical analysis.

Strategy for data synthesis

To calculate a pooled OR or RR with their 95% confidence intervals, we used adjusted ORs or RRs and 95% CIs that reported in individual studies whenever possible. We estimated heterogeneity by using Higgins I^2, which measures the percentage of total variation across studies. I^2 was calculated as follows: $I^2 = 100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom. Negative values of I^2 are defined at zero; I^2 lies between 0% (no observed heterogeneity) and 100% (maximal heterogeneity). An I^2 value greater than 50% was considered to indicate substantial heterogeneity.

When substantial heterogeneity was observed, we used the DerSimonian and Laird method to calculate the pooled RR with 95%CI based on the random-effects model.

Analysis of subgroups or subsets

Subgroup analysis: study design, study region, occupation, shift schedule, dose-response.

Contact details for further information

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Professor Seung-Kwon Myung. National Cancer Center Graduate School of Cancer Science and Policy, South Korea

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

10 September 2019

Anticipated completion date

31 March 2020

Funding sources/sponsors

No funding sources/sponsors

Conflicts of interest

None known

Language

English

Country

South Korea

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms
Breast Neoplasms; Case-Control Studies; Cohort Studies; Humans; Rare Diseases; Shift Work Schedule

Date of registration in PROSPERO
10 January 2020

Date of first submission
27 August 2019

Stage of review at time of this submission
The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
10 January 2020

C. Quality Assessment by the Newcastle-Ottawa Scale

Table. Methodological quality of observational studies based on the NOS: Case-control studies (n = 13)

	Selection				**Comparability**	**Exposure**			
Case-control studies (n=13)	Adequate definition of cases	Represen-tativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonres-ponse rate	**Total**
2001 Davis [5]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
2001 Hansen [81]		☆	☆	☆	☆☆	☆	☆		7
2006 O'Leary [106]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
2010 Pesch [85]	☆	☆	☆	☆	☆☆	☆	☆		8
2013 Fritschi [107]	☆	☆	☆	☆	☆☆		☆		7
2013 Grundy [83]	☆	☆		☆	☆☆		☆	☆	7
2013 Menegaux [108]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
2015 Papantoniou [58]	☆	☆	☆	☆	☆☆	☆	☆		8
2015 Wang [56]	☆	☆		☆	☆☆	☆	☆	☆	8
2018 Yang [57]		☆	☆	☆	☆☆	☆	☆		7
2019 Bustamante-Montes [90]	☆	☆		☆	☆☆	☆	☆		7

2019 Pham [12]	☆	☆		☆	☆☆	☆	☆	☆	8
2020 Szkiela [91]		☆		☆	☆☆		☆	☆	6

Table. Methodological quality of observational studies based on the NOS: Nested case-control studies (n = 4)

	Selection				**Comparability**	**Exposure**			
Nested case-control studies (n=4)	Adequate definition of cases	Represen-tativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonres-ponse rate	**Total**
2006 Lie [82]		☆	☆	☆	☆☆		☆		6
2011 Lie [86]		☆	☆	☆	☆☆	☆	☆		7
2012 Hansen [87]	☆	☆	☆	☆	☆☆		☆		7
2015 Li [111]	☆	☆	☆	☆	☆☆	☆	☆	☆	9

Table. Methodological quality of observational studies based on the NOS: Cohort studies (n = 15)

	Selection				**Comparability**	**Outcome**			
Cohort study (n=13)	Represen-tativeness of exposed cohort	Selection of non-exposed cohort	Ascertain-ment of exposure	No present of outcome of interest at start or study	Comparability of cohorts	Assessment of outcome	Long follow-up enough for outcome	Adequacy of follow-up of cohorts	**Total**
2010 Pronk [63]	☆	☆		☆	☆☆	☆	☆	☆	8
2013 Knutsson [84]		☆		☆	☆☆	☆	☆	☆	7
2014 Koppes [109]	☆	☆	☆	☆	☆☆	☆	☆	☆	9
2015 Akerstedt [110]		☆	☆	☆	☆☆	☆	☆		7
2016 Travis (MWS) [64]	☆	☆		☆	☆☆	☆	☆		7
2016 Travis (EPIC- Oxford) [64]		☆	☆	☆	☆☆	☆	☆		7
2016 Travis (UK BioBank) [64]	☆	☆		☆	☆☆	☆	☆		7
2017 Jørgensen [92]	☆	☆		☆	☆☆	☆	☆	☆	8
2017 Vistisen [93]	☆	☆		☆	☆☆	☆	☆		7
2017 Wegrzyn	☆	☆		☆	☆☆	☆	☆		7

(NHS) [94]								
2017 Wegrzyn (NHS2) [94]	☆	☆	☆	☆☆	☆	☆		7
2019 Jones [95]	☆	☆	☆	☆☆	☆	☆	☆	8
2020 Harris [97]	☆	☆	☆	☆☆	☆	☆		7
2020 McNeil [98]	☆	☆	☆	☆☆	☆	☆		7
2020 Sweeney [96]		☆	☆	☆☆	☆	☆		6

Abbreviations: EPIC-Oxford, The Oxford component of the European Prospective Investigation into Cancer and Nutrition; MWS, Million Women Study; UK, United Kingdom; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II.

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