Occupational Medicine, 2025, **75**, 596–607
https://doi.org/10.1093/occmed/kqaf040

OXFORD

Night shift work and breast cancer risk in healthcare workers: a systematic review and meta-analysis

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Background: Healthcare workers (HCWs) are often exposed to night shift work, which may increase cancer risk.
Aims: We conducted a systematic review and meta-analysis on night shift work and breast cancer risk in HCWs.

Methods: We systematically searched PubMed/Embase, evaluated the risk of bias (RoB) of the included studies, and estimated pooled relative risks (RR) using random-effects models.

Results: Twelve studies were included (12 132 breast cancer cases); 60% of these were rated as 'definitely' or 'probably' high RoB in the exposure characterization domain. Compared to never exposure, pooled RRs were 1.05 (95% confidence interval [CI] 0.96–1.14, 12 studies, I^2 = 39%) for ever, and 1.11 (95% CI 0.96–1.28, 9 studies, I^2 = 62%) for ≥10 years, 1.25 (95% CI 1.01–1.55, 7 studies, I^2 = 59%) for ≥20 years, and 1.68 (95% CI 0.77–3.65, 3 studies, I^2 = 79%) for ≥30 years of night shift work. Pooled RRs were higher in case–control/nested studies and studies assessing lifetime occupational history. The RR for ≥20 years of exposure lost statistical significance in influence analysis and approached unity after correction for possible publication bias.

Conclusions: Long-term night shift work may increase breast cancer risk in HCWs, but the association is far from established. If this association were real, night shift work would be responsible for a substantial number of breast cancers in HCWs.

INTRODUCTION

According to the World Health Organization, the health workforce includes health professionals, health associate professionals, personal care workers in health services, health management and support staff, and other health service providers not elsewhere classified [1]. Worldwide, about two-thirds of those employed in health and social work are women [2].

Healthcare workers (HCWs) may be exposed to several occupational health and safety hazards, including chemical (e.g. antineoplastic agents and other drugs, ethylene dioxide, disinfectants), biological, physical (e.g. radiation, noise, vibration), biomechanical (e.g. patients' handling, awkward postures) and psychosocial (e.g. night shift, verbal abuse and violence, burnout) factors, some of which are potentially carcinogenic. The International Labour Organization reported that millions of HCWs worldwide suffer from work-related illnesses and many die from occupational hazards [3]. In particular, selected studies reported an excess cancer incidence among HCWs [4–7].

HCWs are frequently exposed to night shift work. Night shift work disrupts the circadian rhythms and is associated with short-term health effects such as insomnia, excessive sleepiness and difficulty concentrating [8]. Night work has also been linked to selected long-term chronic conditions, including coronary heart disease and metabolic conditions such as type 2 diabetes, obesity and the metabolic syndrome [9–13].

In 2019, the International Agency for Research on Cancer (IARC) classified night shift work as a probable human carcinogen (Group 2a), based on limited evidence of cancer in humans, sufficient evidence of cancer in experimental animals and strong mechanistic evidence in experimental animals [14]. The largest amount of epidemiological evidence on the carcinogenic effect of night shift work is for breast cancer in females,

Key learning points

What is already known about this subject:

- Healthcare workers are frequently exposed to night shift work, an occupational health and safety hazard.
- In 2019, the International Agency for Research on Cancer classified night shift work as a probable human carcinogen (Group 2a), based on limited evidence of cancer in humans, sufficient evidence of cancer in experimental animals, and strong mechanistic evidence in experimental animals.

What this study adds:

- This systematic review and meta-analysis, based on the most updated evidence, is suggestive of a possible role of long-term night shift work in breast cancer risk in healthcare workers.
- In light of the limitations in the quantification of night work exposure in epidemiological studies and the lack of robustness and statistical significance of meta-analytic results, the association is however far from established.

What impact this may have on practice or policy:

- Given the high prevalence of night shift work among healthcare workers, the excess risk of breast cancer, if real, could contribute to a substantial number of diagnoses among healthcare workers.

with various studies, conducted among nurses and other HCWs or other occupational groups exposed to night shift work, suggesting an increased risk for longer duration and/or intensity of night shift work [15,16]. If real, about 5% of breast cancer cases in women from Britain could be attributed to shift work [17]. The issue has, therefore, major public health relevance, but the evidence remains inconsistent [18,19].

Among recent systematic reviews and meta-analyses on night shift work and breast cancer [20–25], only one [23], updated to 2020, provided a summary estimate of the effect for a population of HCWs (i.e. nurses). It found a pooled relative risk (RR) of breast cancer of 1.14 (95% confidence interval [CI] 0.99–1.3) for night shift work <10 years and of 1.25 (95% CI 0.92–1.70) for night shift work ≥10 years, versus never night shift work. However, that meta-analysis was based on four studies on nurses only (two for the analysis of long-term duration), including a study in which exposure to night work was assumed for all years spent in infirmaries [26], and did not consider other informative studies [18,19,27]. The few available reviews that focused on HCWs did not provide pooled quantitative estimates of the effect [28,29]. In addition, new data became available [30,31].

We conducted, therefore, an updated systematic review and meta-analysis on the association between night shift work and the risk of breast cancer in the female population of HCWs.

METHODS

Data collection and reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis 2020 guidelines [32] and the guidelines for Systematic Review and Meta-Analysis of Observational Studies [33]. The study protocol was registered on PROSPERO (CRD42024497582).

A systematic search of PubMed and Embase was conducted from inception to 23 November 2023. The search strategy was developed using both free text terms and controlled vocabulary terms around the topics of *night shift*, *breast cancer* and *occupation* (Supplementary Methods, available as Supplementary data at *Occupational Medicine* online). In Embase, the search was restricted by excluding conference abstracts and preprints. The reference lists of the selected articles, recent reviews on the topic [20–24] and the IARC Monograph volume 124 on the carcinogenicity of night shift work [34] were screened by hand to identify additional articles.

Each record was screened by two independent investigators with expertise in epidemiology and biostatistics (F.T., F.B., G.E.) at the title and abstract level. The same reviewer team independently performed the full-text review. Reasons for exclusion were systematically recorded. Disagreements were discussed with other investigators (E.N., C.L.V.). Studies were selected if they were cohort, case–control nested in a cohort, or case–control studies, and reported a measure of association (e.g. hazard ratio [HR], odds ratio [OR], relative risk [RR]) between night shift work and female breast cancer in HCWs, or specific categories of HCWs (e.g. nurses). A study that estimated the RR of breast cancer for night shift work in various occupations/industries, including nurses, HCWs and physicians/general practitioners, versus no night shift work in any occupation/industry was also considered but further excluded in a sensitivity analysis [35]. Studies providing results for other occupations/industries (e.g. military women, petroleum workers, flight attendants), or for the general population, or for a mixture of HCWs and women employed in other occupational sectors were not considered unless a risk estimate specific for HCWs was provided. Reviews, case reports, case series, letters, editorials and animal studies were excluded. Studies were also excluded if they were in languages other than English, had a cross-sectional design, analysed breast cancer mortality, considered male breast cancer, or did not provide any measure of association between night shift work and breast cancer risk in HCWs. Studies on sleep pattern, exposure to light at night or chronotype were not considered. In case of overlapping participants across publications, the most updated analysis was selected.

Studies selected for inclusion were assessed for the risk of bias (RoB) using the OHAT Risk of Bias Rating Tool for Human and Animal Studies [36]. The tool is designed to be used for the RoB evaluation in experimental animal and human studies with different study designs, including cohort and case–control studies. The six questions applicable to epidemiological case–control and cohort studies were selected (i.e. 3, 4, 7, 8, 9, 10); these assessed selection bias, confounding, attrition/exclusion bias, detection bias (both for exposure and outcome) and selective reporting. One author (F.T.) rated the studies according to the tool, another author (G.E.) checked the rating and a third author (F.B.) participated in the evaluation in case of disagreement.

Data extraction was performed independently by two investigators (F.T., G.E.). Disagreements were discussed with other investigators (E.N., C.L.V., F.B.) until a consensus was reached. The following data were collected in a predefined datasheet: name of the first author, year of publication, study design, population of HCWs, number of breast cancer cases, cohort size (for cohort studies) or number of controls (for case–control or nested case–control studies), exposure data source, definition of night shift work, estimate of the RRs (e.g. HR, OR) of breast cancer, with the corresponding 95% CIs, for different metrics of night shift work in HCWs, including ever versus never exposure, categories of duration, and type of night shift, and factors adjusted for in the analyses. The RRs obtained from the models with the highest degree of adjustment available in each study were extracted. For the paper by Travis *et al.* [18], which analysed separately three distinct population-based cohorts, we extracted results for the subset of women who had worked as a nurse for ≥10 years in the Million Women Study cohort. Different results were available for the Nurses' Health Study (NHS) II [15] according to various measures of shift work; we used the one based on the cumulative shift work combining baseline and follow-up exposure data.

We investigated the association of ever versus never night shift work (according to original study-specific definitions) and of categories of duration of night shift work versus never night shift work with the risk of breast cancer. For the analysis of ever versus never night shift work, in studies that did not provide the corresponding RR but gave the RRs for different categories of night shift duration or intensity (e.g. occasional, regular) versus never night shift work, we combined such RRs into a single estimate using the method for pooling non-independent estimates within individual studies by Hamling *et al.* [37] or a fixed effect model, according to data availability. In the study by Härmä *et al.* [31] we combined the RRs for follow-up durations <10 and ≥10 years using a fixed effect model. The method for pooling non-independent estimates was also used to combine the RRs for different categories of HCWs in the study by Jones *et al.* [35].

In the analysis on the duration of night work, we estimated the pooled RR for (i) long-term night shift work, defined according to three different cut-offs, i.e. ≥10, ≥20 and ≥30 years; (ii) different categories of duration of night shift work, i.e. <10, 10–20, >20 years; and (iii) each additional year of night shift work (dose-risk meta-analysis). Using the midpoint for closed time categories and 1.2-fold the lower bound for the open-ended upper categories, single numeric values were assigned to each category of duration in each study. In analyses (i) and (ii), the method by Hamling *et al.* [37] was used to combine within studies the RRs referring to durations falling into the different ranges considered. In analysis (i), studies were included in one, two or all the three comparisons according to data availability. In analysis (ii), we included only the four studies which could contribute to all the three categories of duration [15,18,38,39]. In the dose-risk meta-analysis (iii), we used a two-stage approach and assumed a linear relationship between the natural logarithm of the RR and the exposure levels (i.e. years employed in night shift work). We first estimated the linear trend within each study, or, when available, we extracted it from the original publication; then we pooled study-specific estimates using a random-effect model. Study-specific slopes were estimated using generalized least-squares estimation taking into account the correlations between the log RRs (due to the fact that they were estimated using a common referent group) as proposed by Greenland and Longnecker [40]. The method requires the distribution of cases and person-years, person at risk or controls across exposure categories. When such data were not available in the original publications, study-specific trends were estimated using weighted least-squares regression, which assumes independency between the log RRs.

For all the analyses, random-effects models were used to pool study-specific RRs. Heterogeneity between studies was assessed using the χ^2 test and inconsistency was measured using the I^2 statistic.

In sensitivity analyses, we re-calculated the pooled estimates: using fixed effect models; including only studies in which the RR was adjusted for a measure of body weight/body mass index and parity (or studies in which authors did not include such factors in the final models after, however, having checked that they were not confounders of the association); and including only studies adjusting further for family history of breast cancer and benign breast disease.

We also estimated the pooled effect in studies with all RoB items scored as 'definitely' or 'probably' low risk of bias. We performed an influence analysis excluding each study in turn from the meta-analysis to assess the impact of each individual study on the combined estimate. Subgroup analyses were conducted according to study design, geographic region, and lifetime versus partial assessment of the participants' occupational history.

Publication bias (or small study effects, i.e. the tendency of smaller studies to show greater effects than larger ones) was assessed by visual inspection of the funnel plot and applying the test proposed by Egger *et al.* [41]. When publication bias was suggested, trim-and-fill analysis was conducted to obtain an alternative adjusted pooled estimate [42].

Statistical analyses were carried out using the software R version 4.3.2 (*meta*, *dosresmeta*, *metasens* and *metabias* packages).

RESULTS

A total of 806 and 548 records were identified, respectively, in PubMed and Embase. Following the removal of duplicates (n = 304), 1050 titles and abstracts were screened. Of the 70 full-text articles in English assessed for eligibility, 10 were included; another article meeting the inclusion criteria was identified from the reference lists of relevant reviews (Figure 1), for a total of 11 articles[15,18,19,27,30,31,35,38,39,43,44]. They included a total of 12 132 breast cancers from 12 distinct populations/studies, since one report provided results for two distinct cohorts [15]. There were seven cohort studies, one nested case–control study and four case–control studies (including two case–control studies derived from large cohorts, but where exposure was retrospectively assessed) (Table 1). Nine studies were from Europe (two from the United Kingdom [18,35], two from Norway [27,43], one from Denmark [39], one from Finland [31], one from Sweden [30], one from the Netherlands [19], one from Italy [38]) and three from North America [15,44]. Eight studies analysed a specific population of HCWs [15,27,30,31,38,39,43], while four studies were based on unselected populations and gave results on HCWs in subgroup analyses [18,19,35,44]. Six studies included nurses only [15,27,30,39,43].

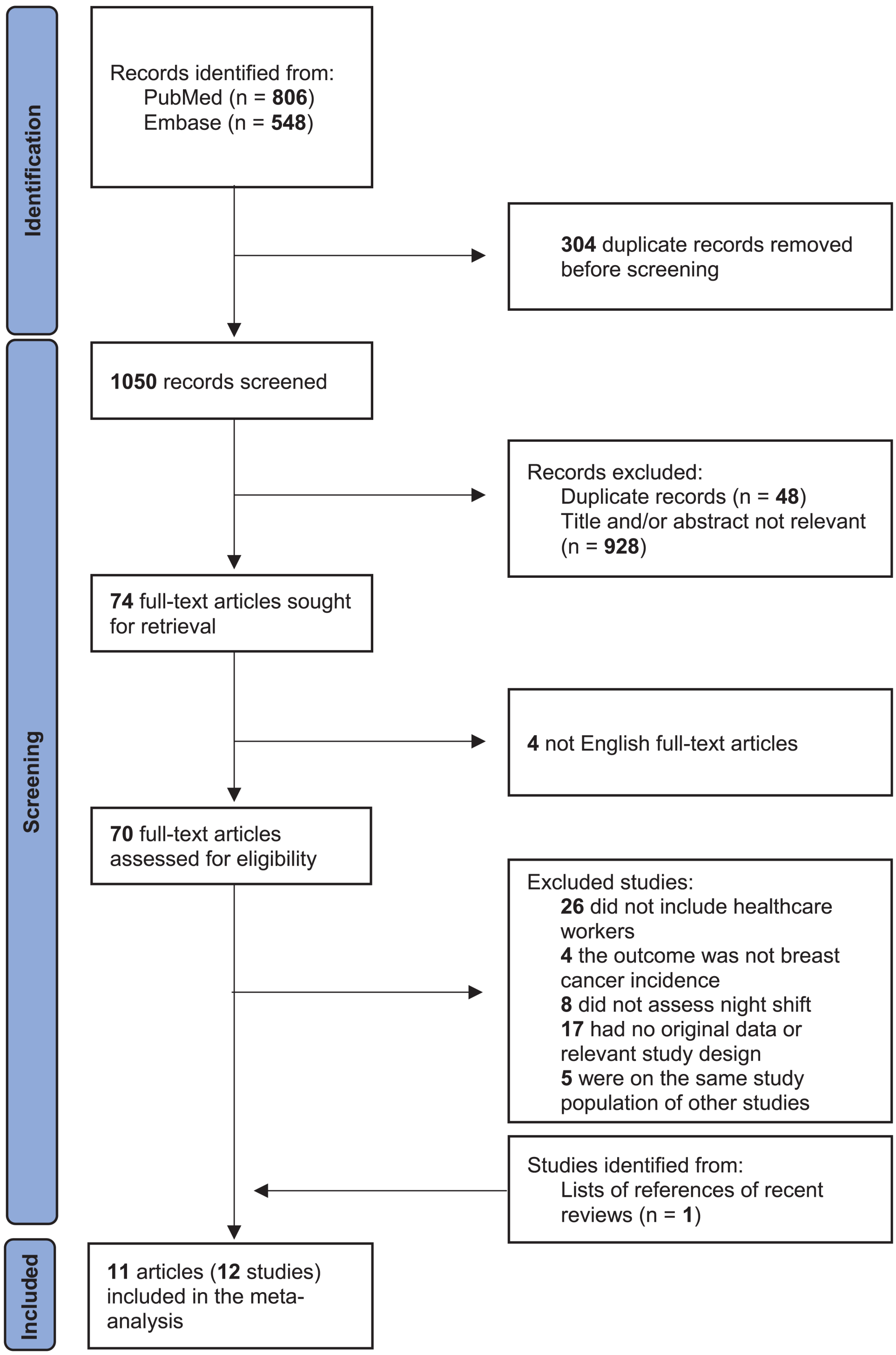

Figure 1. Flow chart for the study selection process.

Information on night shift work was obtained by self-reports from study participants through self-administered questionnaires or interviews in the majority of the studies; a study used employment records [30] and another assigned night work to study participants based on workplace information derived from a nurse registry and census data [27]. Among the cohorts, one had baseline data on the current night shift [19], three baseline data on prior exposure [15,18,31], two both baseline data on prior exposure as well as updated exposure data throughout follow-up [15,35], while one relied on employment records for the study period but had no work history data for the period prior to enrolment [30]. All studies adjusted for, or were matched by, age. Eight of the 12 studies adjusted for some measures of body weight and parity, or at least evaluated the potential confounding effects of such variables; of these, 3 adjusted also for family history of breast cancer and history of benign breast disease.

A summary of the RoB assessment of the studies is given in Table 1 (available as Supplementary data at *Occupational Medicine* Online). Three out of 12 studies (25%) scored 'definitely low' or 'probably low' risk of bias on all the six items. No issue was found concerning selective reporting. Ten out of 12 studies (83%) scored as 'definitely low' or 'probably low' risk of bias on the selection and attrition/exclusion bias items, and 8/12 studies (67%) on confounding. The worst RoB result was related to exposure characterization, with seven studies (58%) judged to have 'probably high' risk of bias, mainly because of self-reported data, and lack of information on full occupational history, particularly in cohort studies.

Based on 12 distinct estimates, the pooled RR for ever versus never night shift work was 1.05 (95% CI 0.96–1.14), with moderate heterogeneity between studies (I^2 = 39%, *p* heterogeneity = 0.08) (Figure 2). In sensitivity analyses, the pooled RR was 1.03 (95% CI 0.99–1.07, I^2 = 39%, *p* heterogeneity = 0.08) from a fixed effect model, 1.05 (95% CI 0.94–1.17, I^2 = 58%, *p* heterogeneity = 0.02) by pooling the eight studies accounting for a measure of body weight and parity, 1.02 (95% CI 0.98–1.07, I^2 = 0%, *p* heterogeneity = 0.44) by pooling the three studies accounting also for family history of breast cancer and history of benign breast disease, and 1.18 (95% CI 0.88–1.58, I^2 = 81%, *p* heterogeneity = 0.01) by pooling the three studies with all RoB items scored as 'definitely' or 'probably' low risk of bias.

No significant association emerged in strata of geographic area, study design and type of exposure assessment, but the pooled RR appeared higher in European than in North American studies, in case–control/nested than in cohort studies, and in studies that assessed lifetime versus partial occupational history (Table 2). In the influence analysis, there was marginal variation in the pointwise pooled estimate, which ranged from 1.02 (95% CI 0.98–1.06) by omitting the study by Hansen and Stevens [39] to 1.07 (95% CI 0.95–1.21) by omitting results from the NHS [15]; the pooled RR was 1.04 (95% CI 0.96–1.13) when excluding the study by Jones *et al.* [35] in which the reference category for the RR was no night shift work in any occupation/industry.

Visual inspection of the funnel plot and Egger's test (*P*-value = 0.473) did not indicate publication bias (Figure 1, available as Supplementary data at *Occupational Medicine* Online).

In the analysis on long-term night work (i), the pooled RR of breast cancer was 1.11 (95% CI 0.96–1.28, based on nine studies) for ≥10, 1.25 (95% CI 1.01–1.55, seven studies) for ≥20 and 1.68 (95% CI 0.77–3.65, three studies) for ≥30 years of night shift work (Figure 3). In all the three analyses, there was appreciable heterogeneity between studies. In subgroup analyses, higher pooled RRs were estimated for European than for North American studies, case–control/nested versus cohort studies, and studies assessing lifetime versus partial occupational history (Table 2). In the influence analysis for ≥20 years of night work, omitting in turn each individual study the pointwise RR estimate ranged between 1.11 and 1.35 and lost its statistical significance 5 times out of 7. In addition, when considering only studies adjusting for body weight and parity the pooled RR was very similar to that of the main analysis (1.24, based on five studies), but lost its statistical significance (95% CI 0.95–1.60, data not shown).

The Egger's test did not indicate significant publication bias in all the three analyses (*P* = 0.192 for ≥10, *P* = for ≥20, and *P* = 0.063 for ≥30 years); however, the funnel plot for the ≥20 years analysis suggested that medium-small negative studies were less likely to be published, and the trim-and-fill corrected pooled estimate approached unity (1.02, 95% CI 0.83–1.25) (Figure 2, available as Supplementary data at *Occupational Medicine* Online).

In the analysis by categories of duration (ii), the pooled RR of breast cancer, based on the same set of studies, was 1.14 (95% CI 0.90–1.45, I^2 = 62%, *P* = 0.05) for <10, 1.17 (95% CI 0.86–1.59, I^2 = 65%, *P* = 0.03) for 10–20, and 1.34 (95% CI 0.91–1.98, I^2 = 68%, *P* = 0.03) for ≥20 years in night shift work (Figure 3, available as Supplementary data at *Occupational Medicine* Online).

According to the dose-risk meta-analysis (iii), each additional year in night work was associated with a 1% increased risk of breast cancer (pooled RR = 1.01, 95% CI 1.00–1.01, I^2 = 63%, *p* heterogeneity < 0.01) (Figure 4).

DISCUSSION

The present systematic review and meta-analysis, based on 12 studies accounting for over 12 000 breast cancer cases, found no material excess breast cancer risk for ever exposure to night shift work among HCWs, but suggested a possible increased risk for long-term exposure. HCW women employed ≥10, ≥20 and ≥30 years in night shift work had, respectively, 11%, 25% and 68% increased breast cancer risk compared to those never exposed, with the estimate for ≥20 years being, however, the only significant result. If real, night shift work would be the major occupational exposure for cancer risk in women [17]. The excess risk for long-term night shift work appeared higher among European, case–control/nested studies, and studies assessing full compared to partial occupational history. The interpretation of a causal relationship is, however, limited by the lack of statistical significance of results from most of the analyses on duration of exposure, the small number of studies contributing to the ≥30 years duration analysis, the lack of robustness of the results for duration ≥20 years following sensitivity analyses and correction for publication bias, and issues in quantifying night work exposure. Of note, major contributors to the overall evidence were the NHS and NHS II cohorts, which accounted together for about 55%, 38% and 43% of the evidence, respectively, in the meta-analyses of ever, ≥10 years, and ≥20 years of night shift work.

We did not perform meta-analyses on other exposure metrics for night work besides duration, since information was available in a few studies only. In a Norwegian nested case–control study by Lie *et al.* [43], a non-significant increase of 10–30% in breast cancer risk was observed when comparing the most extreme categories of cumulative lifetime night shifts and average monthly night shifts. Moreover, nurses with longer duration (≥5 years) of intensive night work (i.e. ≥6 and ≥7 consecutive nights) had a significantly elevated risk of 70–80%. In addition, in a nested case–control study within a nationwide cohort of

Table 1. Characteristics of the studies assessing the association between night shift work and breast cancer risk in healthcare workers included in the systematic review

Study, country	Study design and setting	Population (BC cases: cohort size [cohort], controls [case–control], non-cases [cross-sectional])	Exposure data source	Definition of night shift work	Comparisons	Adjustment factors
Lie *et al.* (2006), Norway	Nested case–control study in a cohort of 44 835 nurses Cases diagnosis: 1960–1982	537:2143 (controls matched by year of birth)	Assignment of night work based on workplace information from the Norwegian Board of Health's registry of nurses and census data (1960, 1970 and 1980) Lifetime exposure		Never versus increasing categories of duration (years)	Total employment time as a nurse and parity
Lie *et al.* (2011), Norway	Case–control[a] study derived from a cohort of 49 402 female nurses Cases diagnosis: 1990–2007	699 (alive in 2009):895 (controls matched by age)	Questionnaire (telephone interview), self-reported Lifetime exposure	Working from at least 12:00 p.m. to 6:00 a.m. In a specific analysis: ≥3 nights/month	Never versus increasing categories of duration (years), cumulative number of night shifts, lifetime average number of night shifts/month, and duration (years) of work in schedules including ≥3, ≥4, ≥5, ≥6 and ≥7 consecutive night shifts	Age, period of diagnosis, parity, family history of BC, alcohol consumption. Age at menarche, OC use, HRT use, BMI at 18 years and at diagnosis, weight gain, smoking and occupational exposure to x-rays were also investigated as potential confounders but according to the authors' evaluation they were not included in the final model
Hansen and Stevens (2012), Denmark	Case–control[a] study derived from a nationwide cohort of 58 091 nurses 2001–2003	267:1035 (controls matched by year of birth)	Questionnaire (telephone interview), self-reported Lifetime exposure	Working after 12:00 p.m. (about 8 hours of work between 7:00 p.m. and 9:00 a.m.) for ≥1 year	Never versus increasing categories of duration (years) and lifetime night shifts Analyses for rotating shift systems	Age, weight regularity, use and duration of HRT, age at menarche, menstrual regularity, menopausal status, age at first birth, family history of BC, breastfeeding
Grundy *et al.* (2013), Canada	Case–control, population-based	138:209 HCWs (of 1134:1179)	Questionnaire (self-administered or telephone interview), self-reported Lifetime exposure	≥50% of time spent on evening and/or night shift	Never versus increasing categories of duration (years)	Age and centre Ethnicity, household income, education, menopausal status, use of fertility drugs, OC use, NSAIDs, antidepressants and HRT use, ever having been pregnant, no. of pregnancies, age at first birth, breastfeeding, age at first mammogram, family history of BC, smoking, alcohol, and BMI were also investigated as potential confounders but according to the authors' evaluation they were not included in the final model
Koppes *et al.* (2014)[b], The Netherland	Cohort Nurses from the Dutch Labour Force Surveys 1996/2009–2009 Average follow-up: ~7 years	182:21 737 nurses	Questionnaire (interview), self-reported Current exposure at baseline	Working between 12:00 p.m. and 6:00 a.m.	No versus occasional and regular night work	Age, origin, children in the house, education, job tenure, contractual working hours
Travis *et al.* (2016), UK	Cohort The Million Women Study[c] 2009/12–2013	399:40 259 nurses for ≥10 years	Questionnaire (mailed), self-reported Data on prior exposure at the 4[f] questionnaire, 12 years after enrolment: lifetime exposure, since women were likely to be retired at that time point	≥3 nights (at any time between 12:00 p.m. and 6:00 a.m.)/month	Never *versus* ever and increasing categories of duration (years)	Age, region, socioeconomic status, parity, age at first birth, BMI, alcohol, strenuous physical activity, family history of BC, age at menarche, OC use, smoking, living with a partner, and use of HRT

Table 1. Continued

Study, country	Study design and setting	Population (BC cases: cohort size [cohort], controls [case–control], non-cases [cross-sectional])	Exposure data source	Definition of night shift work	Comparisons	Adjustment factors
Wegrzyn *et al.* (2017), USA	Two cohorts of nurses NHS: 1988–2012 NHSII: 1989–2013 24 years of follow-up	NHS 5971:78 516 (1 568 438 person-years) NHSII 3188:2 214 525 person-years	Questionnaire (mailed), self-reported NHS: Baseline data on prior exposure NHS II: Baseline data on prior exposure and updated exposure data throughout follow-up	≥3 nights/month in addition to days/evenings in that month[d]	Never *versus* increasing categories of duration (years)	Age, height, BMI, BMI at age 18, adolescent body size, age at menarche, age at first birth, parity, breastfeeding, type of and age at menopause, use and duration of oestrogen-only and combined oestrogen and progesterone HRT, family history of BC, benign breast disease, alcohol, physical activity, current mammography use
Jones *et al.* (2019), UK	Cohort Generations Study 2003/2014–2018 Median follow-up of 9.5 years	112:6 850 000 person-years	Questionnaire, self-reported Baseline data on exposure in the 10-year period before enrolment and updated exposure data (6 years after baseline)	Working regularly in the late evening or night (between 10:00 p.m. and 7:00 a.m.) in the last 10 years	Never versus ever	Age, time since recruitment to cohort, birth cohort, benign breast disease, family history of BC, socio-economic score, birth weight, height at age 20, age at menarche, BMI at age 20 and in post-menopause, age at first pregnancy, parity, breast-feeding, OC use, alcohol, smoking, physical activity, menopausal status, use of HRT, age at menopause
Traversini *et al.* (2020), Italy	Case–control, hospital-based 1997–2016	79[e]: 354	Questionnaire (interview), self-reported Lifetime exposure	NR	Never *versus* increasing categories of duration (years)	Matching factors: age, working health service Adjustment: duration of shift work and night work, job task; other possible confounders were mentioned but not defined
Gustavsson *et al.* (2023), Sweden	Cohort of 25 585 nurses and nursing assistants 2008–2016	299:160 220 person-years	Employment records Exposure data from 2008 for each year	Working ≥3 hours between 10:00 p.m. and 6:00 a.m.	Never versus ever and increasing categories of duration (years)	Age, childbirth, profession, country of birth
Härmä *et al.* (2023[f]), Finland	Cohort The Finnish Hospital Personnel Study 2004/12–2016 Maximum follow-up time: 16.5 years	261:20 763	Questionnaire, self-reported Baseline data on prior exposure	NR	Baseline: day work always versus night shift work Past exposure: day work always versus increasing categories of duration (years)	Age, socioeconomic status, children 0–6 years, children 7–18 years, smoking, alcohol, BMI

Abbreviations: BC, breast cancer; BMI, body mass index; HRT, hormone replacement therapy; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NR, not reported; NSAIDs, non-steroidal anti-inflammatory drugs; OC, oral contraceptives.
[a]This was a case–control study nested in a cohort but was considered as a case–control study since data on night shift work were collected after diagnosis.
[b]The Koppes *et al.* (2014) study analysed the association of night shift work in the general population, but performed a sensitivity analysis among nurses.
[c]The Travis *et al.* (2016) study analysed the association of night shift work in the general population based on data from three cohorts (i.e. The Million Women Study, The EPIC-Oxford and the UK Biobank); results for healthcare workers (women who had worked as a nurse for ≥10 years) were available only for The Million Women Study (40 259 of the 519 062 women in the cohort with available data on night shift work).
[d]The NHS and NHSII investigated rotating night shift work; thus, a nurse working night shifts but not on a rotating shift schedule may have been included in the unexposed group.
[e]Prevalent cases.
[f]The Härmä *et al.* (2023) study analysed the association of shift work among female members of the Finnish Public Sector study, which included a hospital subcohort (i.e. The Finnish Hospital Personnel Study).

Danish nurses, Hansen *et al.* [39] reported an over 2-fold increased breast cancer risk among individuals in the highest tertile of cumulative number of lifetime night shifts. Thus, results on other metrics for night work go in the same direction as, and hence support, our findings about long-term duration of night shift work.

The association between night shift work and breast cancer is not established as well, with various recent meta-analyses providing partially conflicting results. While two of them reported increased risks for ever and longer duration of night shift work [20,24], another meta-analysis found a significant increased risk for short- (< 10 years) but not long-term (> 10 years) night

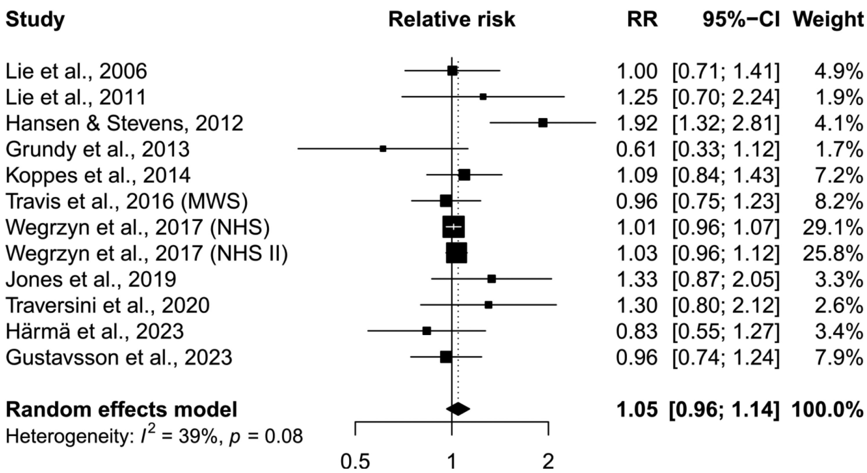

Figure 2. Study-specific and pooled relative risks (RRs) of breast cancer, with corresponding 95% confidence intervals (CIs), for ever versus never night shift work in healthcare workers.

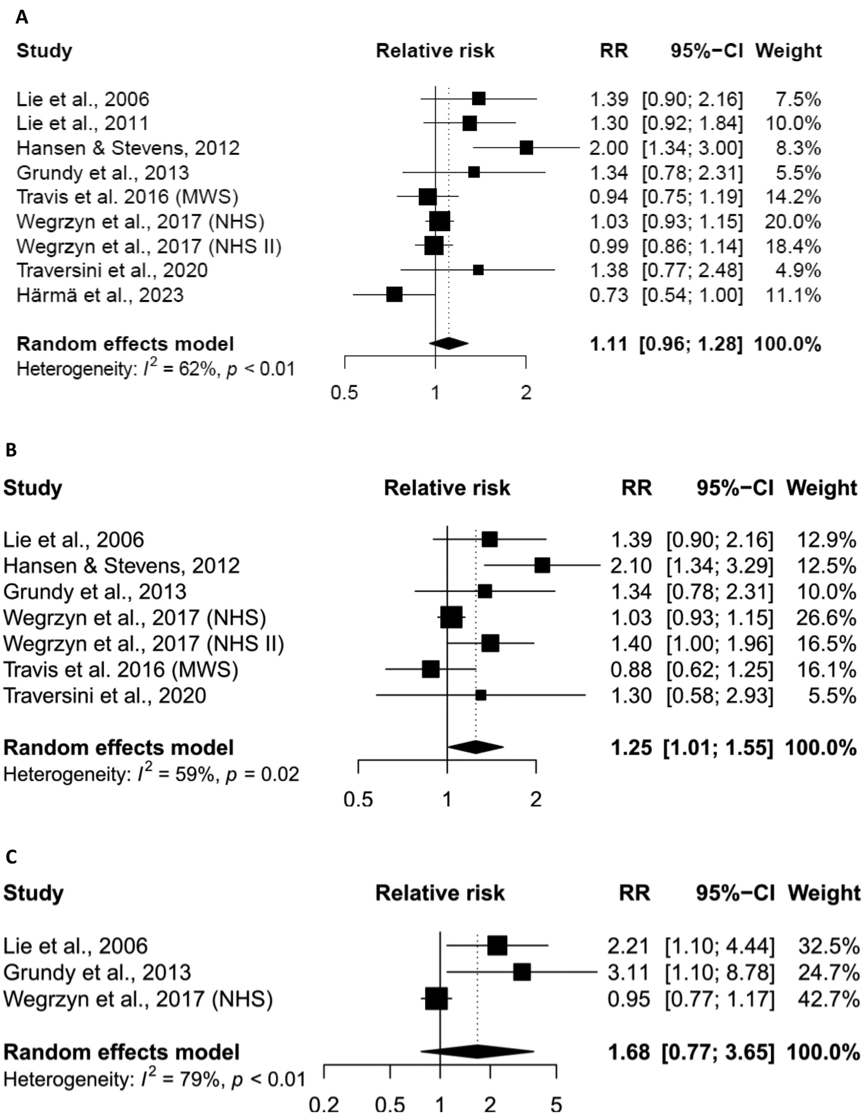

Figure 3. Study-specific and pooled relative risks (RRs) of breast cancer, with corresponding 95% confidence intervals (CIs), for long-term night shift work: ≥10 (Panel A), ≥20 years (Panel B) and ≥30 years (Panel C), versus never night shift work in healthcare workers.

Table 2. Subgroup analyses for the meta-analyses of night shift work and breast cancer in healthcare workers

	Comparison								
	Ever versus never			≥10 years versus never			≥20 years versus never		
	No. studies	RR (95% CI)	I^2; p_{het}	No. studies	RR (95% CI)	I^2; p_{het}	No. studies	RR (95% CI)	I^2; p_{het}
Geographic area									
Europe	9	1.12 (0.96–1.30)	43%; 0.08	6	1.20 (0.89–1.60)	74%; <0.01	4	1.34 (0.88–2.03)	67%; 0.03
North America	3	1.02 (0.95–1.08)	31%; 0.23	3	1.02 (0.94–1.11)	0%; 0.55	3	1.16 (0.93–1.44)	43%; 0.17
Study design									
Cohort	7	1.02 (0.98–1.06)	0%; 0.78	4	0.97 (0.88–1.08)	32%; 0.23	3	1.07 (0.87–1.31)	48%, 0.15
Case–control/ nested	5	1.17 (0.82–1.68)	66%; 0.08	5	1.48 (1.21–1.80)	0%; 0.57	4	1.57 (1.21–2.03)	0%, 0.49
Assessment of the participants' occupational history[a]									
Lifetime	6	1.12 (0.90–1.40)	66%: 0.01	6	1.21 (0.97–1.51)	65%; 0.01	5	1.34 (0.98–1.83)	57%; 0.05
Partial	5	1.01 (0.96–1.07)	0%; 0.59	2	0.90 (0.65–1.25)	76%; 0.04	1	1.03 (0.93–1.15)	–

Abbreviations: CI, confidence interval; RR, relative risk.
p_{het}, *P*-value for heterogeneity among studies.
[a]We did not include in this analysis the study by Lie *et al.* (2006), which considered lifetime occupational history but used the hospital workplace as a proxy for night shift work.

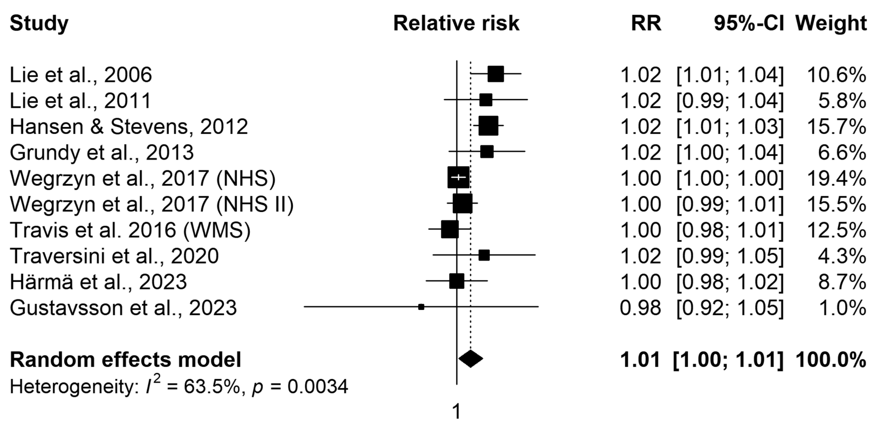

Figure 4. Study-specific and pooled relative risks (RRs) of breast cancer, with corresponding 95% confidence intervals (CIs), for one additional year of night shift work in healthcare workers (two-stage dose-risk meta-analysis).

shift exposure [23], and another one an association with ever exposure and longer duration among overall studies but not among cohort nor nested ones, and concluded that night shift work was not associated with breast cancer risk [22]. The most robust evidence likely derived from a pooled analysis of three large prospective studies (MWS, EPIC-Oxford and UK Biobank) and a meta-analysis of published literature, which reported little or no effect of long-term shift work [18].

A major issue in studies addressing the role of night shift work on health relates to exposure quantification. With the exception of one study [30], all studies collected self-reported work schedule data by means of self-completed or interviewer-administered questionnaires. However, by comparing questionnaires to objective payroll data, Härmä *et al.* [45] reported reasonable validity of various self-reported metrics of night shift work, including permanent day, permanent night work and shift work with nights. The only study included in the present review based on objective employment records was limited by the fact that payroll data were not available before the baseline [30].

Furthermore, night shift work represents a complex exposure, which requires the comprehensive collection of detailed information in epidemiological studies. This includes, among the other factors, the frequency of night work, its duration, intensity, cumulative exposure over time and rotation type [46]. While cohort studies are generally recognized as the gold standard in epidemiological research, case–control studies may be preferable over cohort ones in the field of night shift work since they allow a more detailed and valid exposure assessment and to record the full occupational history of the study participants [47]. On the other hand, cohort studies appear to be more prone to (non-differential) misclassification. An extensive data collection on night shift domains in cohort studies, often designed with a broader focus on various exposures, is logistically complicated by the large number of participants involved and limited questionnaire information. While case–control studies included in this systematic review assessed full occupational history, most of the cohort studies used simple questions to retrospectively collect the cumulative years of night shift work at baseline lacking updated exposure information throughout the follow-up, thus providing a partial assessment of the participants' occupational history. In the study by Jones *et al.* [35], the history of night shift work was only collected over the 10-year period preceding the recruitment of middle-aged adults, with the possibility of missing out exposure in early career, when it is often more common [48]. Additionally, in the study by Koppes *et al.* [19], only current exposure at baseline was recorded. On the other hand, the NHS II collected both baseline and follow-up exposure data [15], and the Million Women Study asked for cumulative years of night work in the fourth follow-up questionnaire, 12 years after enrolment of women aged 50–64 years, and thus it can be reasonably assumed that the study measured lifetime exposure [18].

Non-differential misclassification is likely to bias results towards the null, and this could be particularly relevant when the strength of the association is small, as in night shift work and breast cancer. Along this line, in subgroup analyses, an apparent increased risk was found only among studies which evaluated lifetime night shift work and in case–control/nested studies, with the set of studies contributing to these two categories largely overlapping. In particular, in the analysis of ≥20 years of night work, the pooled RR was 1.57 among case–control/nested studies, and 1.34 in studies considering the full occupational history, suggesting a role of long-term night shift work in breast cancer risk. However, among the case–control/nested studies assessing full occupational history: one Italian study was based on prevalent cases and was rated by the authors as 'definitely high risk of bias' in four over six RoB domains [38]; a Canadian population-based study had a low response rate, particularly among controls, and selected controls within a screening mammography programme, suggesting the potential for selection bias [44]; and a nested case–control study within a cohort of nurses assumed exposure to night work merely for years of working in hospitals and was therefore prone to misclassification [27].

An additional issue in the interpretation of the results is the lack of a clear and consistent definition of night shift work and of the reference group of never-exposed women. In fact, the definition varied so largely across studies that we were not able to define homogeneous subgroups of studies according to this aspect. Three studies did not even provide any detail about the definition of night work while the NHS studies only investigated rotating shifts including night work. Thus, it was not possible to investigate the heterogeneity due to differences in the definition of night shift work. However, a report by the IARC Working Group exploring issues on the definition of shift work in cancer studies reported no relevant differences in the results of epidemiological studies according to the various definitions of shift work [46].

Some occupational, environmental and lifestyle factors could confound or mediate the association between night work and cancer [14]. Working at night has been linked to smoking, obesity, metabolic syndrome, diabetes, high-calorie intake, low levels of physical activity and low socioeconomic status [48–51], suggesting that night shift workers have a more unfavourable risk profile for cancer and chronic diseases in general. An inverse association between night shift work and parity has also been reported [48,50,52]. Overweight/obesity in post-menopause and nulliparity are established risk factors for breast cancer [53,54], and although the association between parity and night work is not well defined, such factors could contribute to the relationship between night work and breast cancer. The results of most of the studies included in the present systematic review were adjusted for several potential confounders, including some metrics of body weight and parity. In sensitivity analyses, the pooled RR did not vary when considering only studies adjusting for body weight and parity, or which evaluated the confounding role of these factors but did not include them in the multiple-adjusted model. Family history of breast cancer and benign breast disease may also have a role. Again, for the ever versus never comparison, we obtained similar results when pooling studies accounting for these additional factors.

In the dose-risk analysis, we consider the linear model because of the small number of studies reporting risk estimates for long duration of exposure. However, the possible association for long-term exposure only suggests a non-linear relationship. Thus, the results from our linear model should be considered with caution.

Different mechanistic hypotheses have been proposed to explain the association between night shift work and breast cancer. One hypothesis is that exposure to light at night and disruption of the circadian rhythm may cause a reduction in the production of melatonin [55], which has a crucial role in regulating several functions in breast cancer pathogenesis, such as apoptosis, cell proliferation, inflammation and angiogenesis [56]. Furthermore, reduced melatonin levels may also generate oestrogen signalling, releasing cancer cells from growth inhibition [57]. This hypothesis is supported by results from a meta-analysis finding lower levels of urine 6-sulfatoxymelatonin (aMT6s), the major urinary metabolite of melatonin, and serum melatonin in night shift workers than day workers [58]. In rats, exposure to light at night suppressed melatonin and increased breast cancer risk [59]. Another mechanism is the shortening of telomerase caused by the disruption of the biological clock; the resulting genome instability has been linked to the development of cancer [60]. Along this line, shorter telomere length has been observed in women with a longer history of night shifts [60,61]. Furthermore, lower serum 25-hydroxyvitamin D [25(OH)D] levels due to sleeping during daytime may partially explain the relationship between circadian disruption and breast cancer [62]. However, while laboratory and animal studies support a protective role for vitamin D, epidemiological evidence on vitamin D and breast cancer is inconclusive [63,64]. Again, sleep disruption may increase oxidative stress [65], which has been linked to the development of various chronic diseases including cancer.

According to these mechanisms, night shift work should increase male breast cancer risk, too. However, epidemiological evidence on this is very limited due to the rarity of the disease. In the Norwegian Offshore Petroleum Workers cohort, there was a suggestion for an excess breast cancer risk in men ever exposed to night shift [66]; however, estimates were not adjusted for possible confounders, except for education, and cohort members were exposed to several other occupational hazards, including some chemical exposures known or suspected to be carcinogenic. Also, the hormonal mechanism could be involved in the night shift–prostate cancer relationship, as highlighted by the IARC [34]; again, the association is still controversial [67].

Night shift work is very common in HCWs due to the provision of 24/7 care [68,69]. Thus, the relatively high excess risk of breast cancer for long-term night work, if causal, would imply that night work is responsible for a sizable breast cancer burden in HCWs. In light of the small RRs associated with the few other modifiable risk factors for the disease, long-term night shift work may represent one of the major preventable predisposing factors of breast cancer in HCWs, and thus a primary target for prevention. Whether night shift can be considered a modifiable and avoidable factor is, in any case, questionable. Using the population attributable fraction methodology, in the general population, 5% of breast cancer cases in Britain [17], 6% in the USA [70], and from 2% to 5% in Canada [69] were attributed to shift work. In the Canadian study, 38% of attributable breast cancer cases would be diagnosed in women employed in health care [69].

In conclusion, the current epidemiological evidence suggests a role of long-term night shift work in breast cancer risk. However, given the limitations in quantifying night work exposure in epidemiological studies and the lack of robustness and statistical significance of most meta-analytic results, the association is far from established. Given the high prevalence of night shift work among HCWs, such excess risk, if real, could contribute to a substantial number of breast cancer diagnoses in HCWs.

COMPETING INTERESTS

None declared.

FUNDING

This work was supported by the Italian Ministry of Health (PNRR-MAD-2022-12376823). CS was supported by the Research Support Plan 2022–2023 from the University of Milan.

DATA AVAILABILITY

The study is based on published data.

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