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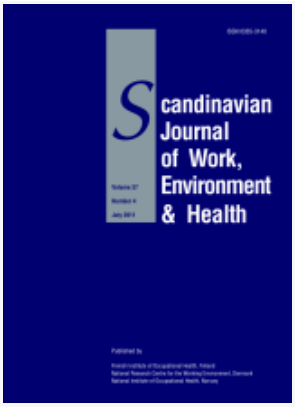

Review

Scand J Work Environ Health 2013;39(5):431-447
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Night-shift work and breast cancer – a systematic review and meta-analysis

by Ijaz S, Verbeek J, Seidler A, Lindbohm M-L, Ojajärvi A, Orsini N, Costa G, Neuvonen K

A doseâ€“response analysis of night-shift work and breast cancer found the evidence insufficient for a causal link. For the first time, quality of the studies was assessed and the results of the review viewed in the light of the quality of evidence. The review calls for studies with prospective follow-up and objective data on night-shift work.

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Key terms: breast cancer; cancer; dose–response; evidence synthesis; meta-analysis; night shift; night-shift work; shift work; systematic review

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Review

Scand J Work Environ Health. 2013;39(5):431–447. doi:10.5271/sjweh.3371

Night-shift work and breast cancer – a systematic review and meta-analysis

by Sharea Ijaz,[1] Jos Verbeek, PhD,[1] Andreas Seidler, PhD,[2] Marja-Liisa Lindbohm, PhD,[3] Anneli Ojajärvi, PhD,[3] Nicola Orsini, PhD,[4] Giovanni Costa, PhD,[5] Kaisa Neuvonen,[6] MSc

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Objective The aim of this review was to synthesize the evidence on the potential relationship between nightshift work and breast cancer.

Methods We searched multiple databases for studies comparing women in shift work to those with no-shift work reporting incidence of breast cancer. We calculated incremental risk ratios (RR) per five years of night-shift work and per 300 night shift increases in exposure and combined these in a random effects dose–response meta-analysis. We assessed study quality in ten domains of bias.

Results We identified 16 studies: 12 case–control and 4 cohort studies. There was a 9% risk increase per five years of night-shift work exposure in case–control studies [RR 1.09, 95% confidence interval (95% CI) 1.02–1.20; I^2=37%, 9 studies], but not in cohort studies (RR 1.01, 95% CI 0.97–1.05; I^2 =53%, 3 studies). Heterogeneity was significant overall (I^2=55%, 12 studies). Results for 300 night shifts were similar (RR 1.04, 95% CI 1.00–1.10; I^2=58%, 8 studies). Sensitivity analysis using exposure transformations such as cubic splines, a fixed-effect model, or including only better quality studies did not change the results. None of the 16 studies had a low risk of bias, and 6 studies had a moderate risk.

Conclusions Based on the low quality of exposure data and the difference in effect by study design, our findings indicate insufficient evidence for a link between night-shift work and breast cancer. Objective prospective exposure measurement is needed in future studies.

Key terms dose–response; evidence synthesis; shift work.

In 2007, an expert group of the International Agency for Research on Cancer (IARC) convened on shift work and its association with cancer. Based on strong animal and weak human evidence, the expert group concluded that night-shift work that involves circadian disruption was probably carcinogenic for breast cancer among women (1).

Using diverse methods and a number of studies, four previous systematic reviews (2–5) concluded that night-shift work could increase the risk of breast cancer, although the evidence was considered limited or weak in three of these. However, none of the reviews took the variation in exposure assessment between studies into account or made an attempt to model the relationship between night-shift work and the risk of breast cancer. In light of the increasing evidence and the lack of rigorous methods in previous reviews, an up-to-date assessment of the association between exposure to night-shift work and breast cancer was undertaken (6).

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Methods

Inclusion criteria

We included studies on working women exposed to night-shift work. The comparison was women in day work. We included studies where the outcome was incidence of breast cancer confirmed by histopathology for ≥90% of the cases or where it would be reasonable to infer the same. We included both retrospective and prospective cohort and case–control studies.

We excluded: (i) airline crew studies because of the additional exposures (cosmic radiation, time-zone changes) and lifestyle factors in this occupation; (ii) studies reporting only mortality, benign breast disease, or other proxy outcomes; and (iii) cohorts where incidence was assessed without differentiating between exposed (to shift work) and non-exposed members. The protocol is available here: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42012002247.

Search, selection and data extraction

We searched Medline, EMBASE, CINAHL, PsycInfo, LILACS, OSH Update and ProQuest dissertation and theses database without date or language restriction. Our search strategy for Medline is presented in figure 1 (7–9).

We checked the references from included studies, existing systematic reviews, and expert commentaries and contacted subject experts and authors of included studies. Two authors independently selected the studies, extracted data, and assessed the risk of bias according to the recommended methods for systematic reviews, with a third person resolving disagreements. Though personal communication with authors, we tried to obtain missing information. Data on night or over-night work were chosen over only evening, early morning, or combined work. When no distinctions were made in the study, we assumed night or over-night work. We chose self-reported exposure over that assessed by a job exposure matrix alone when both were reported separately in a study. Data obtained from authors directly were chosen over data reported in publications or modeled by us.

For each included study, we assessed the risk of bias as low, high, or unclear against ten important sources (domains) of bias by following a validated checklist for measuring bias in studies of risk factors (7–9). Following were the domains where risk of bias was assessed: (i) exposure definition, (ii) exposure assessments, (iii) blinding of assessors, (iv) reliability of assessments, (v) confounding, (vi) attrition, (vii) selective reporting, (viii) analysis methods in the study (research-specific bias), (ix) funding, and (x) conflict of interest.

8) #1 AND #7

7) #2 OR #3 OR #4 OR #5 OR #6

6) (occupational diseases[MH] OR occupational exposure[MH] OR occupational medicine[MH] OR occupational risk[TW] OR occupational hazard[TW] OR (industry[MeSH Terms] AND mortality[SH]) OR occupational group*[TW] OR work-related OR occupational air pollutants[MH] OR working environment[TW])

5) "Work Schedule Tolerance"[Mesh] OR "Personnel Staffing and Scheduling"[Mesh] OR "Circadian Rhythm"[Mesh] OR "Sleep Disorders, Circadian Rhythm"[Mesh] OR "Biological Clocks"[Mesh]

4) ((shift* OR night OR rotat*) AND Work[tiab]) OR "shift work" OR shiftwork[tw] OR shiftwork's[tw] OR shiftworker[tw] OR shiftworker's[tw] OR shiftworkers[tw] OR shiftworkers'[tw] OR shiftworking[tw] OR shiftworks[tw]OR shift roster[tw]

3) ((evening OR night OR extended OR rotat* OR irregular OR fixed OR roster) AND (shift OR shifts)) OR "extended shifts"[tw] OR "extended work shifts"[tw]

2) "Light at night" OR "LAN"[tiab] OR ((circadian OR "biological clock" OR "sleep-wake cycle" OR "sleep-wake schedule") AND disrupt*)

1) Breast AND (cancer OR cancers OR neoplasm OR neoplasms) OR Breast neoplasms [Mesh]

Figure 1. MEDLINE search strategy PubMed May 2012 (last update 10 October 2012).

Exposure definition. If the definition included at least two of the following three aspects recommended by IARC, exposure definition was considered to be at low risk of bias: shift system (rotating or fixed, forward or backward rotation); shift duration (in years); and shift intensity (per week or per month frequency). The study was considered to have a high risk of bias when it used a categorical definition with an arbitrary threshold (eg, 1 year, "ever done night work") *or* a definition that covers only one aspect of exposure (start or end time of shift or duration, intensity, or shift system).

Assessment of exposure. If objectively measured (direct measurement of exposure, such as logging data, shift schedule data from the human resources or employers' records, and prospective self-measurement of exposure, eg, diaries), a study was considered to have a low risk

of bias in the assessment of exposure. The risk of bias was considered to be high if the exposure was assessed using subjective measures: reported by participants (interviews/questionnaires) or a proxy used to allocate exposure status (job matrix, job title).

Blinding. A study was given a low risk judgment on blinding if assessors were reported or indicated to be blind to exposure status in cohort studies and to case status in case–control studies. A high risk judgment was given when either it was reported or indicated in the report that assessors were not blind to exposure or case status for cohort and case–control studies respectively.

Reliability of exposure estimates. When good inter/intra observer reliability was achieved with reported reliability values or when objective measures were used (such as log data), cohort studies' reliability of exposure estimates were judged to have a low risk of bias. A study was considered to have a high risk in this domain when observer variability was reported by means of a subjective judgment of reliability. A lack of information was given a judgment of unclear.

Confounder assessment. We assessed confounding on two levels: whether 4 of the 5 major confounding factors/effect modifiers [age, body mass index (BMI), ethnicity, parity (number of children, age at first birth), and socioeconomic status] were assessed completely (low risk) or assessed partially (high risk), and if confounders were measured with valid methods (low risk) or not (high risk). As a rule, we gave a low risk judgment overall when both categories were marked low risk. However it was also marked low risk if two reviewers agreed that, even though one aspect was considered unclear or high risk, the results of the study were not affected by this factor: for example, when ethnicity was not assessed in a study but it was clear that ethnic variation in the sample was minimal.

Attrition. A total loss of participants (non-response in case–control studies) of ≥20% *or* a dropout/non-response difference between the compared groups of ≥10% *or* the reasons for dropout/non-response not given/different led to a judgment of high risk. Conversely a <20% loss in total and ≤10% difference in dropout/non-response between the two groups was considered low risk. A lack of information led to a judgment of unclear.

Selective reporting of results. This domain was given a high risk judgment if authors presented incomplete/selective reporting of the tested hypotheses (compared to aim and objectives) *and/or* crude estimates only. A low risk grade was given when adjusted estimates were presented for all hypotheses tested as per aims, and unclear was given when not enough information was available or the hypothesis was unclearly stated.

Research-specific bias. This pertains to the analysis conducted in the study and includes three aspects: (i) the methods used to reduce bias due to research design (these methods include standardization, matching, adjustment in multivariate model, stratification, and propensity scoring), (ii) the assessment of dose–response in some way (subgroup, regression), and (iii) author justification of the sample size, in descending order of importance. When all three of these were at low risk of bias or two reviewers agreed that unclear or high risk in one of these aspects in a particular study did not affect the results significantly, the whole domain was given a low risk judgment. Authors were contacted to clarify any ambiguity.

Funding. This was assessed in two areas: source of funding and the involvement of the funding body in the research. When a study was funded by non-profit organization(s) and it was clear that the funding body was not involved in the conduct or interpretation of the research, it was considered to have low risk of bias. If one of these factors was high risk, the study was considered to have a high risk of bias; if one of these was not reported, the study was marked as having an unclear risk.

Conflicts of interest. A study was considered to have a (i) low risk of bias if there were no conflicts of interests to be declared or if declared interests were not deemed conflicting (as assessed by two reviewers), (ii) high risk if one or more authors had indicated a conflicting interest, and (iii) unclear when the information was not provided.

Bias prioritization

For the overall assessment of the risk of bias per study, we had a consensus that exposure to shift work schedules have the most relevant impact on the biological rhythm, circadian de-synchronization and re-adjustment, as well as sleep deprivation and recovery, thus on health. Exposure definitions and assessments were, therefore, obviously the most important domains for risk of bias in our review. Similarly the analysis and the confounders taken into consideration may affect more significantly the reliability of a study in the context of the current review than, for example, blinding. Therefore, we placed the domains into two hierarchical groups. Major domains of bias: (i) exposure definition, (ii) exposure assessment, (iii) reliability of assessments, (iv) confounding, and (v) analysis methods in the study (research-specific bias). Minor domains of bias included: (i) blinding of assessors, (ii) attrition, (iii) selective reporting, (iv) funding, and (v) conflict of interest.

We then rated the study-level risk of bias as: low (low risk in all major domains and ≥2 of the minor domains), moderate (low risk of bias in ≥4 major and 2 minor domains), or high risk of bias (low risk of bias in <4 major domains)

The detailed form is available in appendix A, www.sjweh.fi/data_repository.php.

Confounders

The complete set of confounders for shift work and breast cancer relationship can be seen in the directed acyclic graph (DAG) presented in figure 2. The appropriate adjustment set for estimating the total effect of shift work on breast cancer would include: age, ethnicity, parity, socioeconomic status, all of which are factors that causally influence shift work as well as breast cancer. We decided to adjust for these confounders and additionally for other potential confounders that were a major risk factor (30% increased risk) for breast cancer and were found to be differentially associated with shift work. The final adjustment set therefore was: age (1, 11, 12), ethnicity (1, 13, 14), socioeconomic status (or a proxy) (10, 15–17), parity (16, 18–21) with adjustment done for either number of children, or age at first child, and body mass index (BMI) (overweight, obese) (22–24).

Some factors although significant for breast cancer were not found to be associated with shift work. Alcohol consumption for example, a known, albeit weak, risk factor for breast cancer was not differentially associated with night-shift compared to day workers and thus was not considered as an important confounder (25–27).

Statistical analysis

We performed a dose–response analysis in a two stage procedure. First, we estimated a dose–response curve for individual studies. We started by assigning a single dose to each shift work exposure category reported in a study (28). For six studies where we got information from authors, we used doses as advised. We used STATA, release 12 (StataCorp, College Station, TX, USA) to calculate study-level incremental risks (29, 30).

In the second stage, we combined the study-specific estimates with a random effects meta-analysis model for trend estimation. Several mechanisms have been hypothesized in literature with at least some evidence of a biological plausibility for night-shift work having a causative link to breast cancer (31). We were limited to analyze exposures as measured in the studies. Studies usually reported the total number of years in night-shift without distinguishing between continuous and interspersed exposure years, indicating an assumption that the effect is because of the total exposure years. We assumed the same for this review. Furthermore, two studies reporting risk per year of night work indicated a very small effect estimate for one year. We therefore took five years (irrespective of intensity or continuity) as an exposure long enough to show a meaningful difference in effect, and 300 shifts an equivalent to maximum intensity night work for one year (6 shifts per week=288 shifts), as the best proxy for the circadian disruption related to night-shift work. We present the risks for five years and 300 night-shift increases, respectively, as the most relevant biological doses for subgroups of case–control and cohort studies.

We took both odds ratios (OR) and risk ratios (RR) as valid estimates of the relative risk because of the low incidence of breast cancer.

We assessed statistical heterogeneity with the I^2 statistic. We performed a meta-regression analysis in STATA with the following pre-specified study level effect modifiers: occupation, site of the study, type of shift system, and study design. We tested our model assumptions in a-priori defined fixed effect analysis and by exclusion of high risk studies.

We tested our choices for assigning a dose to the open ended highest categories by capping the ≥20 years highest exposure categories using the lowest bound of the category as the dose value. In some previous studies, authors reported increased risk with only very long exposures (5, 16, 32). Thus a linear model would not hold. We therefore tested the assumptions underlying the dose–response relationship by fitting a cubic spline model with various knots, and by using the natural logarithm of the dose for the exposure to see if this improved the goodness of fit.

We tried to avoid reporting biases by including studies irrespective of language and publication status and by contacting authors. We assessed publication bias by observing funnel plot asymmetry and performing the Egger's test to ascertain bias due to small studies (33).

We used the approach of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine and the GRADE approach (supplementary appendix B, www.sjweh.fi/data_repository.php) for grading the quality of the total evidence (34).

Results

Search results

Sixteen studies (16, 32, 35–47) met our inclusion criteria. Of these, 12 were included in the meta-analysis of exposure duration and 8 in that of number of night-shifts (figure 3). Characteristics of the 16 included studies are presented in tables 1a, b, and c. [Supplementary appendix C contains 4 ongoing studies, 2 papers await-

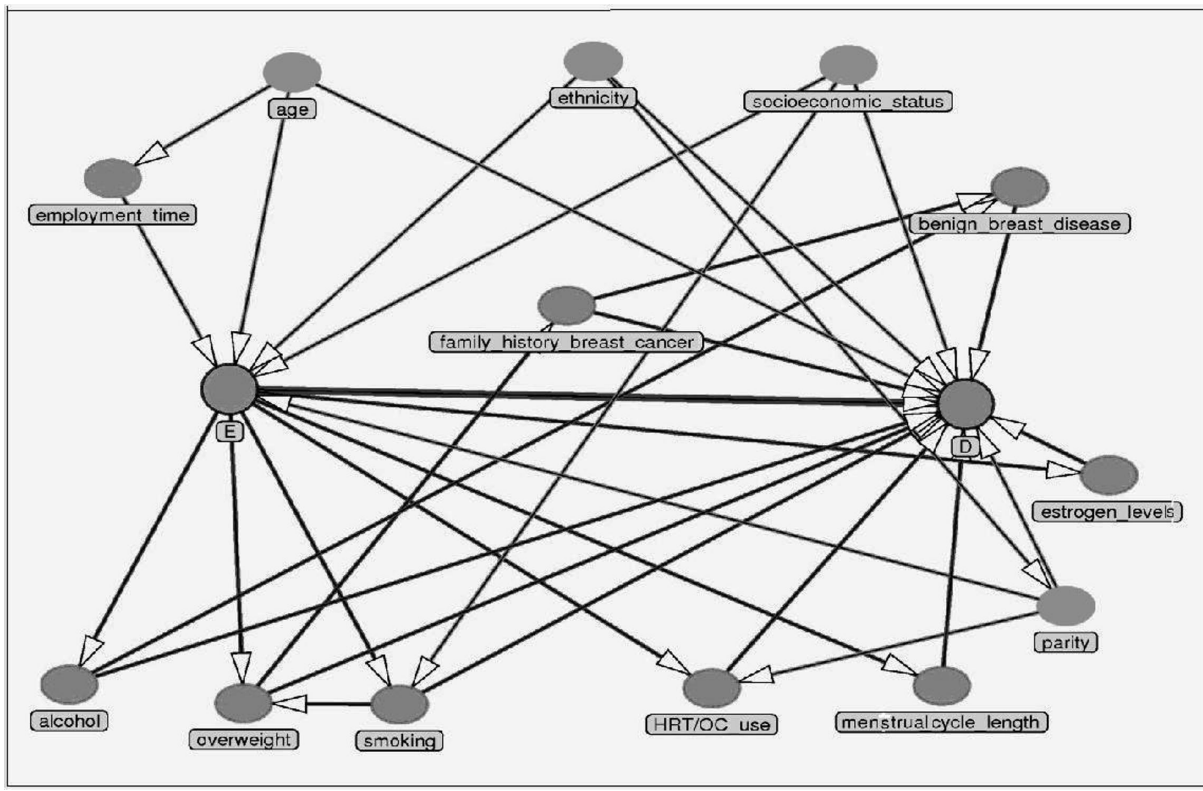

Figure 2. Directed acyclic graph (DAG) for shift work and breast cancer. [HRT/OC=Hormone replacement therapy/oral contraceptives]

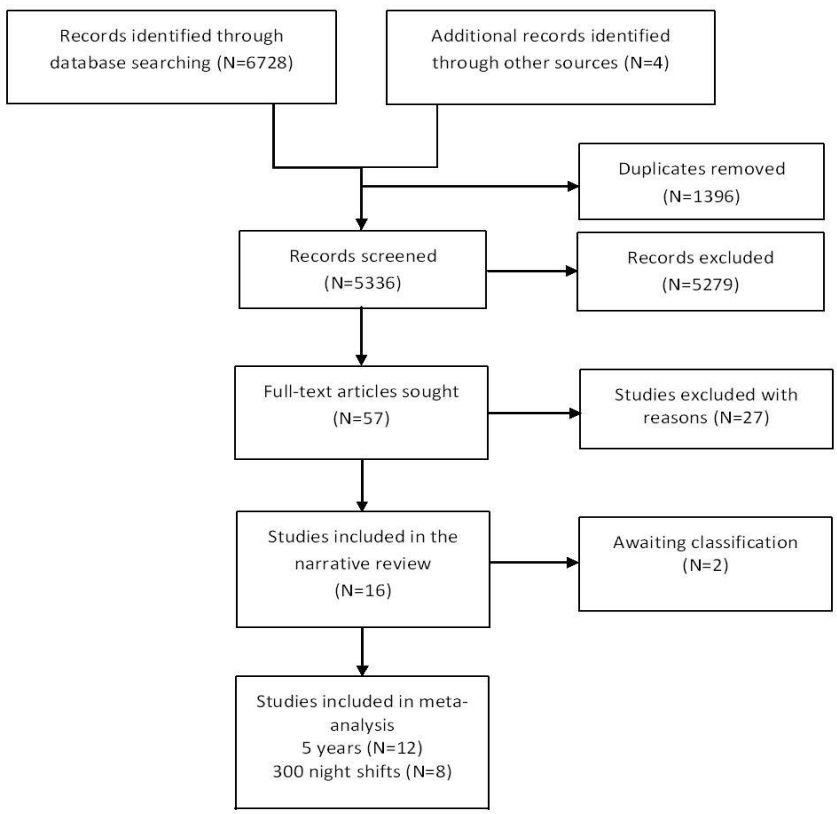

Figure 3. Study flow diagram.

Table 1a. Characteristics of included studies

Study	Design	Sources of participants	Number of participants (analyzed)	Mean age years	Occupation	Location	Exposure: source of information
Davis et al 2001 (35)	Population-based case–control	Cases from population-based cancer registries	Total 1510 Cases 767 Controls 741	47	Various	USA	Interviews
Hansen 2001 (36)	Nested case–control	Danish Cancer Registry cases identified by linkage to pension fund records	Total 12 305 Cases 6281 Controls 6024	42	Various	Denmark	Employment histories from files of pension fund
Hansen et al 2011 (48)	Nested case–control	Danish Nurses Association; cases linked to Danish Cancer Registry	Total 1302. Cases 267 Controls 1035	<70	Nursing	Denmark	Interviews
Hansen et al 2012 (37)	Nested case–control	Danish military; cases linked to Danish Cancer Registry	Total 637 Cases 132 Controls 505	<70	Military	Denmark	Questionnaires / interviews
Knutsson et al 2012 (38)	Cohort, prospective	Women in the WOLF (Work, Lipids, and Fibrinogen) cohort	Total 3060. Exposed 549 Controls 2511	41	Various	Sweden	Questionnaires
Li 2011 (39)	Nested case–control	Textile factories of the Shanghai Textile Industry Bureau (STIB)	Total 6489 Cases 1709 Controls 4780	48	Textile industry	China	Factory personnel records, interviews
Lie et al 2006 (32)	Nested case–control	Norwegian Board of Health's registry of nurses	Total 2680 Cases 537 Controls 2143	27–85	Nursing	Norway	Norwegian Board of Health's registry of nurses
Lie et al 2011 (40)	Nested case–control	Norwegian Board of Health's registry of nurses	Total 1594 Cases 699 Controls 895	54.5	Nursing	Norway	Interviews
Menegaux et al 2012 (41)	Population-based case–control	Hospitals in two French departments	Total 2549 Cases 1232 Controls 1317	49	Various	France	Interviews
O'Leary et al 2006 (42)	Population-based case–control	Residents of Nassau and Suffolk counties on Long Island, New York, from EBCLIS study	Total 996 Cases 487 Controls 509	55.6	Various	USA	Interviews
Pesch et al 2010 (43)	Population-based case–control	Women from the Greater Region of Bonn, Germany (GENICA Study)	Total 1539 Cases 746 Controls 793	56	Various	Germany	Interviews
Pronk et al 2010 (44)	Cohort, prospective	Representative urban communities of Shanghai	Total 69 472 Exposed 18 234 (cases 73) Unexposed 51 238 Cases 276	52.5	Various	China	Interviews and job exposure matrix
Schernhammer et al 2001 (16)	Cohort, prospective	Female registered nurses enrolled in the Nurses' Health Study	Total 78 562 Exposed 46 801 Unexposed 31 761 Cases 2441	55	Nurses	USA	Questionnaires
Schernhammer et al 2006 (45)	Cohort, prospective	Female registered nurses enrolled in the Nurses' Health Study II	Total 113 216 Exposed 78 063 Unexposed 35 153 Cases 1352	40	Nurses	USA	Questionnaires
Schwartzbaum et al 2007 (46)	Cohort, retrospective	Randomly sample of gainfully employed people in 1960 and 1970 population censuses	Total 1 148. 661 Exposed 3057 Unexposed 1 145 604 Cases 98	57	Various	Sweden	Census and Annual Survey of Living Conditions
Tynes et al 1996 (47)	Nested case–control	Norwegian Telecom cohort	Total 309 Cases 50 Controls 259	52	Radio/ telegraph operator	Norway	Norwegian seamen registry

Table 1b. Characteristic of included studies: Exposure [SD=standard deviation]

Study	Shift work description	Exposure definition	Reference category definition	Exposure duration (mean, years)	Exposure intensity (mean shifts per month)	Shift system
Davis et al 2001(35)	Graveyard shift	Beginning work after 19:00 and leaving work before 09:00 hours.	0 years worked ≥1 graveyard shift per week	Cases: 4.5 Controls: 3.1	Not reported	Not reported
Hansen 2001 (36)	Trades in which ≥60% of the female responders worked at night	At least half a year in trades with predominantly (≥60%) night work	Employed in trades with <40% night work	Not reported	Not reported	Not reported
Hansen et al 2011 (48)	Working outside normal daytime hours, nightshift work, graveyard shift	Night-shift: from 23:00–24:00 to 07:00–8:00 hours; Graveyard shift: about 8 hours of work between 19:00–09:00 hours for one year	Permanent day or day-evening work	Cases: 11.9 Controls: 10.9	Not reported	Rotating and fixed
Hansen et al 2012 (37)	Night shift work	Working ≥1 year during hours beginning after 17:00 and ending before 09:00 hours; permanent and rotating night-shifts assessed as one	Women with <1 year of night work	Not reported	Not reported	Rotating and fixed
Knutsson et al 2012 (38)	Shift work, night-shift work	Shift work with night work on ≥1 occasion; shift with night work: "22:00–06:00 hours" at baseline, "about 18:00–06:00 hours" at follow-up	If data indicated day work on all occasions when the subject participated; day work: 06.00–18.00 hours	9.39 (SD) 9.53	Not reported	Backward rotating, forward rotating and fixed
Li 2011 (39)	Rotating night-shift work	Working continuously between 12:00– and 05:00 hours in a rotating shift schedule	Day work only, non-shift work only	Cases 12.9 years	Not reported. Calculated 8.6 nights per month	Rotating
Lie et al 2006 (32)	Night work	Nurses working at infirmaries	Managerial jobs, teaching, and work at physiotherapy or outpatients' departments	Cases 16.7 Controls 15	Not reported	Not reported
Lie et al 2011 (40)	Night work	Working periods from rotating, as well as permanent, night schedules. Includes the work of permanent night workers; A "night-shift" was a shift that lasted from ≥24:00–06:00 hours	Nurses who never worked at night after graduation	75% of controls has <12 years exposure	Not reported	Rotating and fixed
Menegaux et al 2012 (41)	Night work	Worked for ≥1 hour between 23:00–05:00 hours. Included night work period, beginning and ending date, number of nights per week, overnight: shift of 6 consecutive work hours or more spanning the time period 23:00–05:00 hours	Never worked at night	Controls 4.5 years median	Controls median 12 nights per month. Cases not reported	No assessment of shift systems
O'Leary et al 2006 (42)	Shift work, evening shift, overnight-shift	Overnight-shifts: could start as early as 19:00 hours and continue until the following morning	Never held jobs involving shift work	Not reported	Not reported	Not reported
Pesch et al 2010 (43)	Night-shift work	Work between 24:00–05:00 hours	Day work only; ever employed never night work	Not reported	Not reported	Not reported
Pronk et al 2010 (44)	Night-shift work	Starting work after 22:00 ≥3 times a month for >1 year.	Never did shift work	Not reported	Not reported	Not reported
Schernhammer et al 2001 (16)	Rotating night-shift work	Years in rotating night-shifts with ≥3 nights per month in addition to days or evenings.	Never worked on rotating night-shifts	Not reported	6.5 per month	Rotating
Schernhammer et al 2006 (45)	Rotating or permanent night work	Years worked rotating night-shifts with ≥3 nights per month in addition to days or evenings and/or years worked permanent night-shifts for ≥6 months	Never worked rotating or permanent night-shift	Not reported	6.5 per month	Rotating and fixed
Schwartzbaum et al 2007 (46)	Shift work	Workplace with a rotating schedule with ≥3 possible shifts per day or had work hours during the night (any hour between 01:00–04:00 hours) ≥1 day during the week preceding the interview.	People in occupation–industry combinations in which <30% were shift workers	Not reported	Not reported	Rotating and fixed
Tynes et al 1996(47)	Shift work	Shift work highly reflects frequent presence in the radio room both at night and during the day, with possible exposure to light at night.	"Shift work none"	Not reported	Not reported	Not reported

Table 1c. Characteristics of included studies: effect estimation and confounder adjustment [BMI=body mass index; OR=odds ratio; IRR=incremental relative risk; RR=relative risk; HR=hazard ratio; SES=socioeconomic status; SIR=standardized incidence ratio]

Study ID	RR per exposure versus no exposure	RR per exposure duration	RR per duration + intensity of exposure [a]	Effect estimate	Adjusted for				
					Age	Parity	BMI	SES	Ethnicity
Davis et al 2001 (35)	Yes	Yes	0	OR, IRR	Yes	Yes	No	No	No
Hansen 2001 (36)	Yes	No	0	OR	Yes	Yes	No	Yes	Yes
Hansen et al 2011 (48)	Yes	Yes	2	OR, IRR	Yes	Yes	Yes	Yes	Yes
Hansen et al 2012 (37)	Yes	Yes	1, 2	OR	Yes	Yes	Yes	Yes	Yes
Knutsson et al 2012 (38)	Yes	No	0	HR	Yes	Yes	Yes	Yes	Yes
Li 2011 (39)	No	Yes	2	HR	Yes	Yes	No	No	Yes
Lie et al 2006 (32)	No	Yes	0	OR	Yes	Yes	No	No	Yes
Lie et al 2011 (40)	No	Yes	1,2	OR	Yes	Yes	Yes	No	Yes
Menegaux et al 2012 (41)	Yes	Yes	1,2	OR	Yes	Yes	Yes	Yes	Yes
O'Leary et al 2006 (42)	Yes	Yes	1	OR	Yes	Yes	No	Yes	No
Pesch et al 2010 (43)	Yes	Yes	2	OR	Yes	Yes	Yes	Yes	Yes
Pronk et al 2010 (44)	Yes	Yes	1, 2	RR	Yes	Yes	Yes	Yes	Yes
Schernhammer et al 2001 (16)	No	Yes	3	RR	Yes	Yes	Yes	Yes	Yes
Schernhammer et al 2006 (45)	No	Yes	3	RR	Yes	Yes	Yes	Yes	Yes
Schwartzbaum et al 2007 (46)	Yes	No	0	SIR	Yes	No	No	Yes	Yes
Tynes et al 1996 (47)	No	No	1	OR	Yes	Yes	No	No	No

[a] 0=no, 1=RR for duration and intensity reported, 2=RR for lifetime night-shifts reported, 3= RR for lifetime night-shifts calculated based on intensity data obtained from authors.

ing full-texts and 27 excluded studies, www.sjweh.fi/data_repository.php].

Study characteristics

The studies included 4 prospective cohort studies (16, 38, 44, 45) where participants were followed for between 5–12.4 years, 12 retrospective studies, including 7 nested case–controls studies (32, 36, 37, 39, 40, 47, 48), 1 retrospective cohort (46), and 4 population-based case–control studies (41–44).

Five studies addressed nurses. One study each focused on radio and telegraph operators, military personnel, and textile factory workers. Seven considered various occupations. Participants ranged in age from 20–85 years (tables 1a, b, and c).

Exposure definitions mostly included start and end times and duration in years. Frequency of shifts per week or month was part of the definition in five studies. Four studies included the shift system as part of the exposure definition. None included all three aspects advised by the IARC (shift system, years of shift work, and shift intensity) (49).

Ten studies reported exposure as binary categorical data (yes versus no shift work). Twelve studies reported categories of increasing years of exposure and two reported increasing duration with increasing frequency categories. Six studies reported cumulative lifetime number of shifts for various exposure levels. Of the five confounding factors, age and parity were adjusted for most often. Eight studies adjusted for all five confounders (table 1c).

No study had an overall low risk of bias and six studies were of moderate risk (37, 39–41, 44, 48) (table 2 and appendix D on www.sjweh.fi/data_repository.php). The same six studies had a low risk of bias in how they defined night-shift work. For method of exposure measurement, only one study used objective exposure assessment from prospectively collected records and consequently had a low risk of bias (39). Thirteen studies (16, 32, 35–37, 39–45, 48) were considered to have a low risk of bias for reliability of exposure assessment. Ten studies had a low risk of bias in adjustment for confounding factors (16, 36–38, 40, 41, 43–45, 48) and ten studies had low risk in the analysis domain (16, 32, 37, 39–41, 43–45, 48). Nine studies had a low risk of bias for blinding (16, 36, 37, 40, 43–46, 48) and nine had low risk in the domain of attrition (16, 32, 36, 39, 41, 42, 44, 45, 47). Authors confirmed that sponsors had no role in conduct or reporting of 12 studies while 13 reported no conflict of interest or this was confirmed by the authors.

Effects of exposure

No specific dose relationship between the exposure and the risk of breast cancer in the individual studies was

Table 2. Risk of bias in and across included studies. [HR=high risk of bias; LR=low risk of bias; UR=unclear risk of bias]

Risk of bias domains	Davis et al 2001 (35)	Hansen 2001 (36)	Hansen et al 2011 (48)	Hansen et al 2012 (37)	Knutsson et al 2012 (38)	Li 2011 (39)	Lie et al 2006 (32)	Lie et al 2011 (40)	Menegaux et al 2012 (41)	O'Leary et al 2006 (42)	Pesch et al 2010 (43)	Pronk et al 2010 (44)	Schern-hammer et al 2001 (16)	Schern-hammer et al 2006 (45)	Schwartz-baum et al al 2007 (46)	Tynes et al al 1996 (47)
Exposure definition	HR	HR	LR	LR	HR	LR	HR	LR	LR	HR	HR	LR	HR	HR	HR	HR
Exposure assessment	HR	HR	HR	HR	HR	LR	HR	HR	HR	HR	HR	HR	HR	HR	HR	HR
Reliability of exposure assessment	LR	LR	LR	LR	UR	LR	LR	LR	LR	LR	LR	LR	LR	LR	HR	UR
Analysis/re-search spe-cific bias	HR	HR	LR	LR	HR	LR	LR	LR	LR	UR	LR	LR	LR	LR	HR	HR
Confounding	HR	LR	LR	LR	LR	UR	HR	LR	LR	HR	LR	LR	LR	LR	HR	HR
Attrition	HR	LR	HR	HR	HR	LR	LR	HR	LR	LR	HR	LR	LR	LR	HR	LR
Blinding of assessors	UR	LR	LR	LR	UR	UR	HR	LR	HR	UR	LR	LR	LR	LR	LR	HR
Selective reporting	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	LR	HR
Funding	UR	LR	LR	LR	LR	UR	LR	LR	LR	UR	LR	UR	LR	LR	LR	LR
Conflict of interest	UR	LR	LR	LR	LR	UR	LR	LR	LR	LR	LR	LR	LR	LR	LR	UR

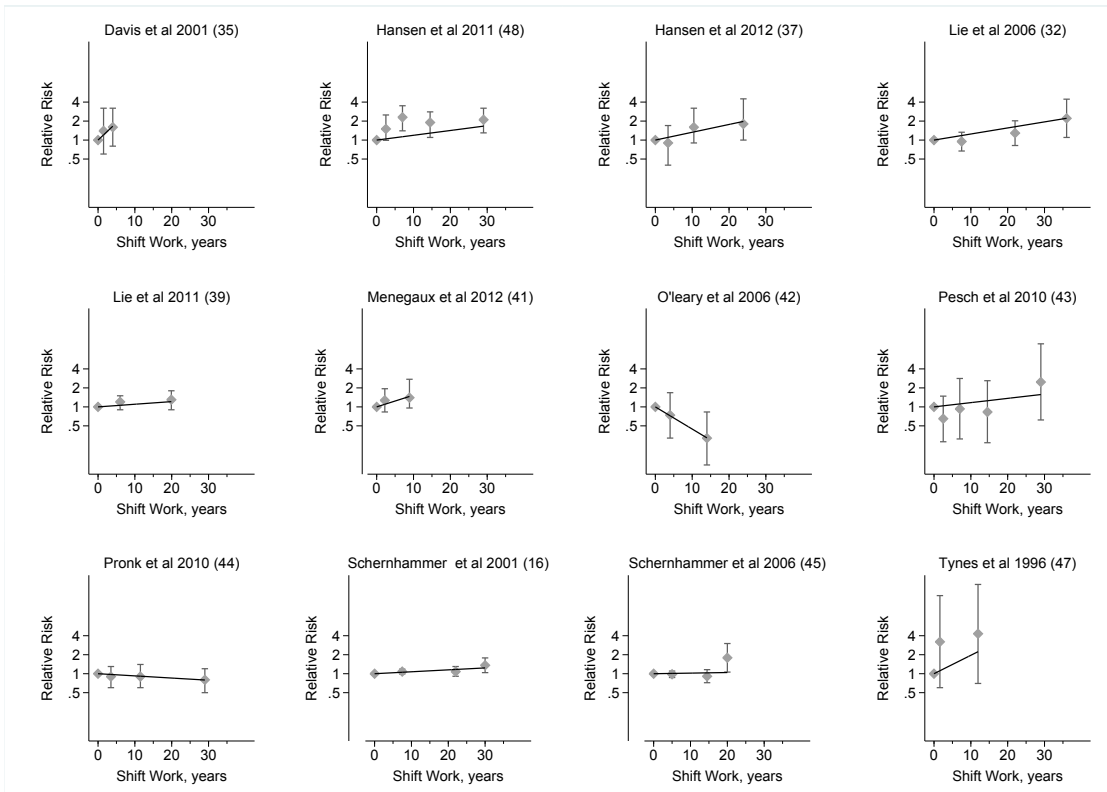

Figure 4. Individual study dose–response graphs showing dose–response in included studies - years of night-shift work (x axis) for relative risk for breast cancer (y axis). The diamonds with confidence intervals represent the reported risks from each exposure category in the study with the dose that we assigned that category (midpoint for all close ended categories). Straight trend lines indicate the dose-response relation as calculated with the general least squares method for trend estimation. Cohort studies with prospective exposure assessment: Pronk et al 2010, Schernhammer et al 2001, Schernhammer et al 2006; the other studies are case–control studies.

Table 3. Exposure categories and their respective calculated doses, reported and transformed risk estimates from studies included in the meta-analysis [95% CI=95% confidence interval; NE=Not estimable; NR=not reported]

Study	Categories of exposure	Risk reported		Dose for categories calculated	Incremental risk per year reported		Incremental per 5 year risk calculated		Incremental per 300 nightshifts risk calculated	
		RR	95% CI		RR	95% CI	RR	95% CI	RR	95% CI
Davis et al 2001 (35)	Ref	1	-	0	1.13	1.01–1.27	1.88	0.82–4.3	NE	
	1–2	1.4	0.6–3.2	1.5						
Years	≥3	1.6	0.8–3.2	4						
Hansen et al 2011 (48)	Ref	1	-	0	1.018	1.010–1.027	1.09	1.02–1.17	1.11	1.05–1.17
	1–4	1.5	0.99–2.5	2.5						
Years	5–9	2.3	1.4–3.5	7						
	10–19	1.9	1.1–2.8	14.5						
	≥20	2.1	1.3–3.2	28						
Hansen et al 2011 (48)	Ref	1	-	0						
	1–467	1.6	1.0–2.6	434						
Number of shifts	468–1095	2.0	1.3–3.0	781.1						
	≥1096	2.2	1.5–3.2	1722						
Hansen et al 2012 (37)	Ref	1	-	0	NR		1.15	0.99–1.33	1.10	1.02–1.18
	1–5.9	0.9	0.4–1.7	3.45						
Years	6–14.9	1.6	0.9–3.2	10.45						
	≥15	1.8	1.0–4.5	23.9						
Hansen et al 2012 (37)	Ref	1	-	0						
	1–415	0.8	0.4–1.9	208						
Number of shifts	416–1560	1.4	0.7–2.9	988						
	≥1561	2.3	1.2–4.6	2705						
Lie et al 2006 (32)	Ref	1	-	0	NR		1.12	1.03–1.20	NE	
	1–14	0.95	0.67–1.33	7.5						
Years	15–29	1.29	0.82–2.02	21.5						
	≥30	2.21	1.10–4.45	36						
Lie et al 2011 (40)	Ref	1	-	0			1.04	0.97–1.14	1.02	0.98–1.07
	1–11	1.2	0.9–1.5	6						
Years	≥12	1.3	0.9–1.8	19.9						
Lie et al 2011 (40)	Ref	1	-	0						
	<1006	1.2	0.9–1.6	503.5						
Number of shifts	≥1007	1.2	0.9–1.7	2012						
Menegaux et al 2012 (41)	Ref	1	-	0	NR		1.21	1.01–1.45	1.03	0.96–1.1
	0.03–4.4	1.27	0.83–1.94	2.2						
Years	4.5+	1.40	0.96–2.04	8.9						
Menegaux et al 2012 (41)	Ref	1	-	0						
	1–663	0.92	0.45–1.89	332						
Shifts	1–1121	1.59	0.86–2.96	561						
	46–1342	2.09	1.26–3.45	694						
	1388–2267	0.91	0.55–1.50	1827.5						
O'Leary et al 2006 (42)	Ref	1	-	0	NR		0.66	0.48–0.93	NE	
	1–7	0.74	0.32–1.68	4						
Years	≥8	0.32	0.12–0.83	14						
Pronk et al 2010 (44)	Ref	1	-	0	NR		0.96	0.89–1.03	0.97	0.92–1.02
	1–5	0.9	0.6–1.3	3						
Years	6–17	0.9	0.6–1.4	11.5						
	≥18	0.8	0.5–1.2	29						
Pronk et al 2010 (44)	Ref	1	-	0						
	1–579	0.9	0.6 –1.3	288.5						
Number of shifts	577–1632	1	0.7–1.5	1104.5						
	≥1633	0.7	0.4 –1.1	2688						

Continued

Table 3. Exposure categories and their respective calculated doses, reported and transformed risk estimates from studies included in the meta-analysis [95% CI=95% confidence interval; NE=Not estimable; NR=not reported]

Study	Categories of exposure	Risk reported		Dose for categories calculated	Incremental risk per year reported		Incremental per 5 year risk calculated		Incremental per 300 nightshifts risk calculated	
		RR	95% CI		RR	95% CI	RR	95% CI	RR	95% CI
Pesch et al 2010 (43) Years	Ref	1	-	0	NR		1.08	0.88–1.3	1.06	0.9–1.25
	1–4	0.64	0.34–1.24	2.5						
	5–9	0.93	0.41–2.15	7						
	10–19	0.91	0.38–2.18	14.5						
	≥20	2.49	0.87–7.18	29						
Pesch et al 2010 (43) Number of shifts	Ref	1	-	0						
	1–807	0.65	0.34–1.26	404						
	≥808	1.73	0.71–4.22	1614						
Schernhammer et al 2001 (16) Years	Ref	1	-	0	NR		1.04	1–1.07	1.0 [a]	1–1.05
	1–14	1.08	0.99 – 1.18	7.5						
	15–29	1.08	0.90 – 1.30	22						
	≥30	1.36	1.04 – 1.78	30						
Schernhammer et al 2001 (16) Number of shifts @6.5 nights per month	Ref	1	-	0						
	78–1092	Not reported	Not reported	585						
	1170–2262	Not reported	Not reported	1716						
	≥2340	Not reported	Not reported	2340						
Schernhammer et al 2006 (45) Years	Ref	1	-	0	NR		1.01	0.94–1.08	1.01 [a]	0.96–1.06
	1–9	0.98	0.87–1.10	5						
	10–19	0.91	0.72–1.16	14.5						
	≥20	1.79	1.06–3.01	20						
Schernhammer et al 2006 (45) Number of shifts@6.5nights per month	Ref	1		0						
	78–702	Not reported	Not reported	390						
	780–1482	Not reported	Not reported	1131						
	≥1560	Not reported	Not reported	1560						
Tynes et al 1996 (47)Years	Ref	1		0	NR		1.40	0.75– 2.6	NE	
	0.1–3.1	0.3	0.1–1.2	1.6						
	≥3.2	0.9	0.3–2.9	11.9						

[a] From unpublished data

seen (figure 4). The transformation of data is presented in table 3.

The meta-analysis of 12 studies showed a significant relative risk increase for working at night for five years (RR 1.05, 95% CI 1.01–1.10, I^2=55%) (figure 5). There was no risk increase in the cohort studies (RR 1.01, 95% CI 0.97–1.05, I^2=34%) but the RR was 1.09 (95% CI 1.02–1.20, I^2=45%) for case–control studies.

For 300 night shifts, the meta-analysis of eight studies indicated a similar association with breast cancer (RR 1.04, 95% CI 1.00–1.10, I^2=58%) (figure 6). The RR for cohort studies was 1.00 (95% CI 0.97–1.04, I^2=53%) and for case–control studies 1.07 (95% CI 1.00–1.10, I^2=37 %).

Three cohort studies (38, 39, 46) and one case–control study (36) could not be included in our meta-analysis because of insufficient data (table 4) to allow calculation of a 5-year exposure risk. These studies, with the exception of Li (39), did not report duration categories of exposure. If control numbers become available, the addition of the Li study to our analysis would improve the precision of our results.

When we looked at the effect of the type of occupation, site of study, and shift system (rotating, fixed, rotating and fixed together) simultaneously, none were significantly related to the risk for breast cancer in the meta-regression analysis. The results of fixed effect analyses were similar to random effects analyses with narrower confidence intervals. The test for non-linearity was non-significant (P>0.05) with log dose, quadratic dose, and cubic splines models fitted in all studies. The linear model fitted the data of the included studies best.

Restricting the result to the moderate risk studies (ie, those of better quality) did not change the results. Five years of night work gave a relative risk of 1.06 (95% CI 0.98–1.14) and for 300 night-shifts it was 1.05 (95% CI 0.95–1.16). The differences between case–control and cohort studies were retained.

A sensitivity analysis in which we capped the highest exposure categories to their lowest bound did not change the results.

Median exposure in the case–control studies was 4 years and the predicted relative risk at this exposure in a post-hoc analysis was 1.07 (95% CI, 1.02–1.12). Median

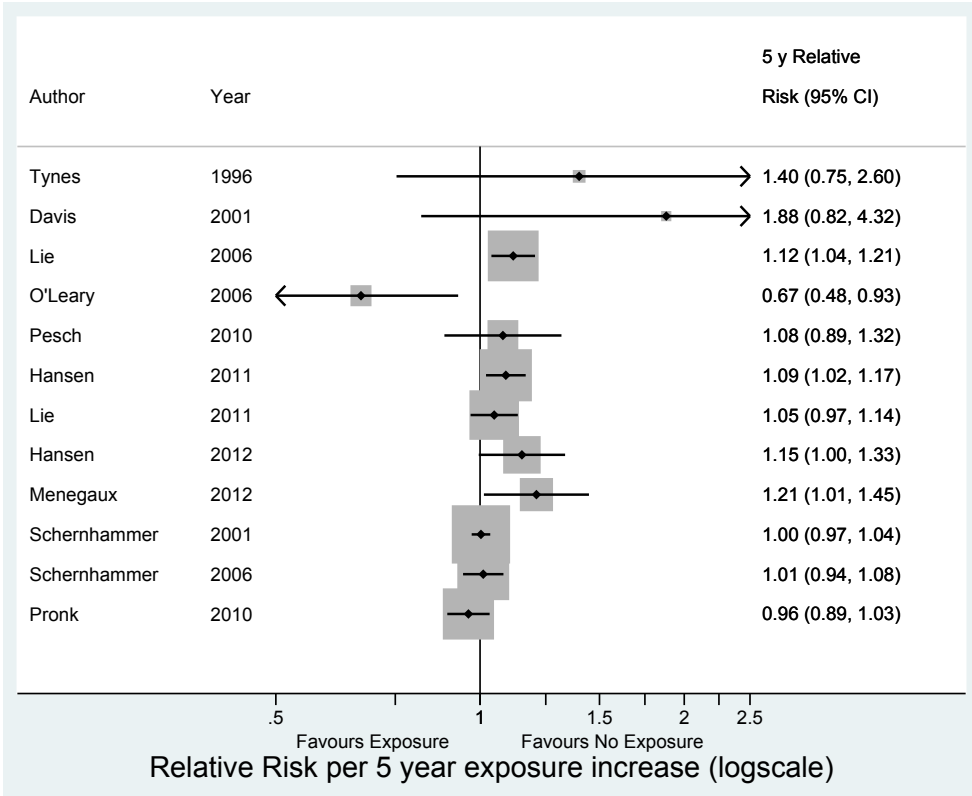

Figure 5. Meta-analysis 5 years of shift work: 12 studies. Overall RR 1.05 (95% CI 1.01–1.10); cohort studies RR 1.01 (95% CI 0.97–1.05); case–control studies RR 1.09 (95% CI 1.02–1.20)

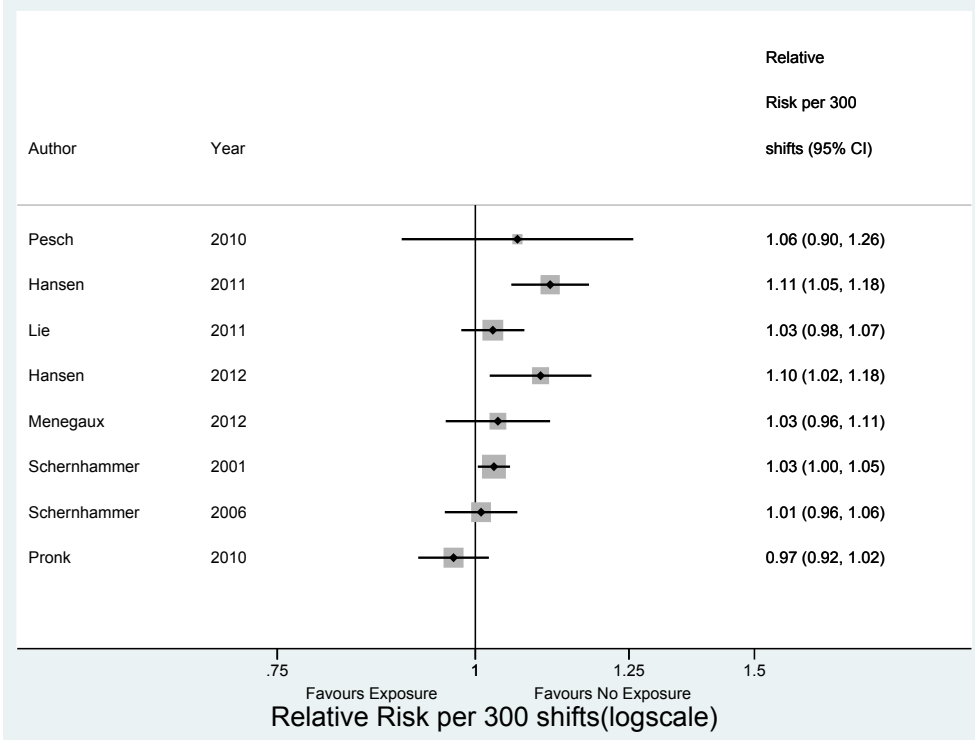

Figure 6. Meta-analysis 300 shifts: 8 studies. Overall RR 1.04 (95% CI 1.00–1.10); cohort studies RR 1.00 (95% CI 0.97–1.04); case–control studies RR 1.07 (95% CI 1.00–1.10).

Table 4. Studies not included in meta-anlaysis. [HR=hazard ratio; 95% CI=95% confidence interval]

Study	Risk	Shift work measure	Reason for not including in meta-analysis
Knutsson et al 2011 (38)	HR 2.02 95% CI 1.03–3.9	Shift work with night work reported on ≥1 occasion	Risk for duration (years exposed) not available
Li 2011 (39)	HR 0.94 95 % CI 0.72–1.22	Rotating night work – increasing exposure categories in years and shifts	No information on number of controls for the various categories
Schwarzbaum et al 2007 (46)	SIR 0.97 95% CI 0.67–1.40	Those marked shift workers in both 1960 and 1970 census	Risk for duration (years exposed) not available
Hansen 2001 (36)	OR 1.50 95% CI 1.30–1.73	At least half a year in trades with predominant (>60%) night work	Risk for duration (years exposed) not available

exposure in the three cohort studies was 9.5 years with a relative risk of 1.02 (95% CI, 0.97–1.10).

The funnel plot represented in figure 7 indicates that small studies might be missing on the side of no effect. However the Egger test was not significant (Egger's coefficient=0.94 (95% CI -0.7–2.6; P=0.24).

Using the GRADE method (34), we judged the evidence to be of very low quality. According to the approach of the Danish Occupational Medicine Association on grading the strength of causality, there is insufficient evidence of a causal association (grade 0).

Discussion

Based on a meta-analysis of 12 of the 16 included studies, we found an average 5% incremental relative risk increase with 5 years of night-shift work. However, cohort studies showed a very small, non significant risk of 1% as opposed to 9% average in case control studies. Different exposure models or sensitivity analyses did not change these results.

Our search was comprehensive, and there was no strong indication of publication bias from Egger's test. Many studies were conducted in Scandinavia where the issue of breast cancer and night-shift work seems to be a topic of debate. Quite a few of these were register-linked studies. However there exist many more such registers worldwide that remain untapped and, therefore, we believe that the included studies alone could form an incomplete picture (50). Many studies referred to nurses and few to the general population and, therefore, it is likely that the results are more applicable to nurses. Similarly most studies were from high income, white populations and thus the pooled results apply largely to these. Of the four studies that could not be included in the meta-analysis, only one (39) had adequate exposure assessment, which interestingly is part of a thesis not yet available as a journal publication. The addition of this large, nested, case–control study would have increased the precision of our results.

We consider the overall quality of the evidence to be low. The most important risk of bias in the studies included in the review was exposure measurement. Exposure to shift work measured by interview or questionnaires has been shown to be influenced by respondent characteristics in a recent study (51). We do not know of other validation studies on night-shift work exposure assessment by self-report. Some improvements in validity could be achieved with repeated questionnaires, as was done in two cohort studies (38, 45). Use of self-report complemented by expert assessment/categorization could similarly improve the validity of exposure assessment in case–control studies (52). A job exposure matrix is a useful tool in epidemiological studies for assessing variation in exposure across jobs. However, since night-shift work exposure varies within an occupation, we believe that this method alone is too imprecise. It is conceivable that retrospective exposure assessment of shift work in interviews or questionnaires, as was the case in most case–control studies, would be subject to recall bias. Especially now, when the association of shift work and breast cancer has gained a lot of publicity, one could imagine that a woman with breast cancer better recalls and reports her shift-work exposure than a woman without breast cancer.

The cohort study design generally provides less biased results for causality especially when the exposure has been ascertained before the disease has occurred. We found exposure assessment of sufficient quality in only one study, a nested case–control study by Li (39). Knutsson et al (38) had probably the most comprehensive prospectively collected questionnaire data but this valuable information was not put to use when categorizing exposure for analysis. Therefore, Li (39) is probably the more reliable, albeit including only Chinese participants. Asian women, based on an unknown genetic disposition, may be less at risk for breast cancer (14).

It is a common assumption in observational epidemiology that it can always be predicted which direction the effect size would change (inflate or attenuate) as a result of bias. We however concur with Rothman et al (53, 54) that this is not the case. We had planned to adjust for bias at study level due to confounding using the methods prescribed by Greenland et al (29), however this was possible for only one study due to lack of relevant data.

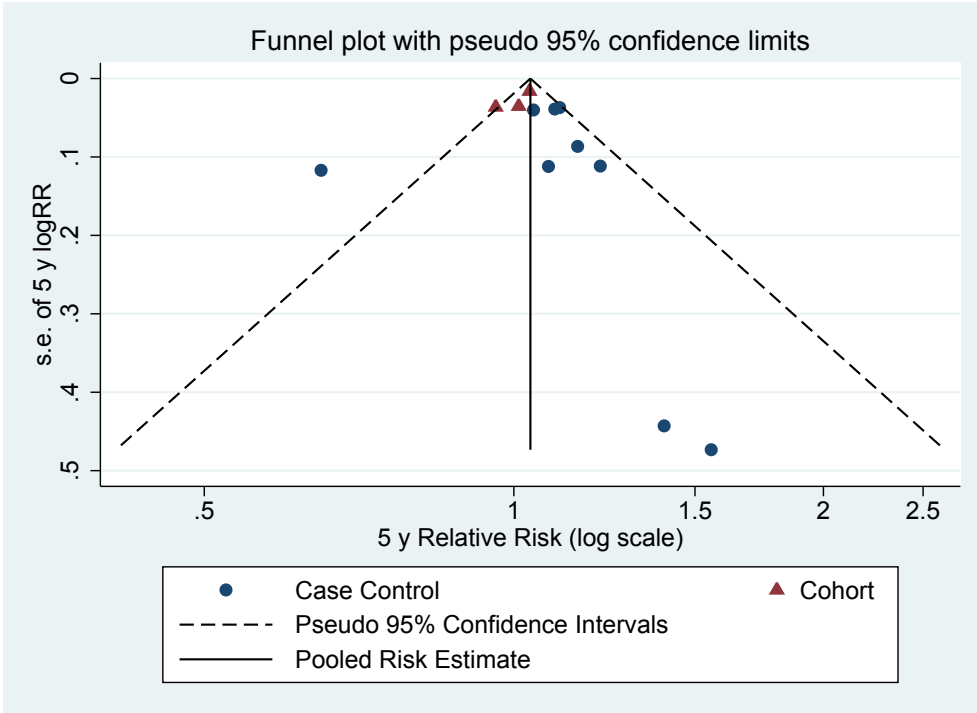

Figure 7. Funnel plot of 12 studies included in the meta-analysis of 5-year risk.

We took the risk of bias into account by conducting a sensitivity analysis.

Limitations

We used an established method of modeling category-specific risk estimates into an incremental risk estimate assuming a linear dose–response. Based on additional information from study authors, we found that our model was accurate in all except the highest usually open category, where it overestimated the dose. However, a post-hoc sensitivity analysis using the lowest dose for these categories did not change the results. We tested our model assumptions by applying cubic splines and log transformation of dose and found the results unchanged. We could not take into account any latency period because only one study assessed it, finding no increase in risk when adjusting for a lag of 10 and 20 years of exposure to rotating night shifts (39).

Over-adjustment for confounding in studies is a problem like under-adjustment. However, we consider the effect of any potential over-adjustment to be minimal because, for many of these established confounders of breast cancer, the association with night-shift work is weak.

It was not possible to examine and draw a conclusion on intensity of night-shift work or permanent night-shift work in our meta-analysis. We did not have a real cumulative index in which both duration and intensity of exposure were measured. It would be good to develop such an index. Finally, the future addition of ongoing studies to these results should improve the precision of our findings.

Agreements with other studies and reviews

In contrast to the previous reviews (2–5), this review followed an priori protocol comparing night-shift with day work. Our review includes 4–8 more studies than previous reviews. None of the previous reviews modeled the dose–response relationship appropriately, in individual studies, to inform the choice of a dose–response model or tested these assumptions.

Besides this, we performed a formal risk of bias assessment for the included studies and incorporated these assessments in the analysis and conclusions drawn where none of the other reviews did so. We consider this extremely important as the quality of the studies, especially in exposure assessments, was the major factor in coming to clear conclusions.

Our findings are different from the reviews of Megdal et al (4) and Erren et al (3) with respect to the strength of the association. Kamdar et al (2) found a relative risk of 13% for up to eight years of night work, close to our findings, but this included flight crew studies in addition to night-shift studies. Kolstad's review (5) did not include a meta-analysis, although a later publication indicated a non-significant risk (RR 1.02 95% CI 0.92–1.13) (55). This meta-analysis included at

least one study outside our inclusion criteria, and it was not clear which estimates from each study were entered in the analysis.

Implications for practice and research

Based on the low quality of evidence and the difference in effect estimate by study design, there is insufficient evidence for a link between night-shift work and breast cancer. For the same reasons we cannot rule out a relationship between the two. The uncertainty is largely due to less-than-valid exposure measurement and can only be resolved by means of better data in the future. Evidence from the two moderate risk Chinese studies indicates no increased risk for this population.

We need studies in which exposure is measured in an objective way before the disease has occurred, ideally in cohorts with long, prospective follow-up. Validation studies of interview/questionnaire data are needed as well to find out if and, to what extent, recall bias occurs.

Conflict of interest

The authors declare: financial compensation from the Danish Work and Environment Fund for J Verbeek, S Ijaz, G Costa and A Seidler for their work towards this project; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years for any author; no other relationships or activities that could appear to have influenced the submitted work.

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