Correlations between permanent night-shift work and/or recurring night-shift work and the development of breast cancer (Cancer Mammae)

A systematic review

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English Summary

Night-shift work is among the most prevalent occupational exposures that occur over a wide range of occupations. It is postulated that light at night suppresses melatonin levels which in turn lowers the anti-estrogen effect of melatonin and would thus result in a higher risk of breast cancer. There is insufficient evidence from previous research to implicate night-shift work in causing breast cancer.

Objective: We did a systematic review and meta-analysis to assess the strength of association between exposure to night-shift work or recurring night-shifts and incidence of breast cancer.

Methods: Multiple databases and non-electronic sources were systematically searched to identify case-control and cohort studies involving females in night-shift work. The comparison was non-shift or day work and the outcome was incident breast cancer. We assessed studies for risk of bias using a content specific piloted checklist on 10 domains of interest. We performed random effects meta-analysis and meta-regressions of study-specific incremental relative risks to determine the risk of cancer associated with a 5 year and 300 night-shift increases in exposure.

Results: We included 16 studies (12 case-control and four cohorts). None of the studies were at a low risk of bias. Random effects meta-regression of dose response using generalized least square estimates from 12 studies showed that night-shift work for 5 years leads to a small significant incremental risk increase in case-control studies (RR1.09; 95% CI 1.02 - 1.2) not in cohort studies (RR 1.01; 95% CI 0.97 - 1.05). Risk with 300 night-shifts was 1.04 (95% CI 1 -1.10). Sensitivity analysis using fixed effect model, various dose response models or including only studies at moderate risk of bias did not change these results. Based on the Danish Occupational Medicine Society's approach the strength of the evidence was insufficient for presence or absence of causality.

Conclusion: There is insufficient evidence from 16 epidemiological studies that night-shift work increases the risk for breast cancer. Better exposure assessment in future studies is needed.

Danish Summary

Sammenhænge mellem permanent nathold arbejde og / eller tilbagevendende natarbejde arbejde og udviklingen af brystkræft (Cancer mammae): En systematisk gennemgang

Resumé

Nat-skifteholdsarbejde er blandt de mest udbredte erhvervsmæssige eksponeringer over en bred forekommende vifte af erhverv. Hypotesen er, at lyset om natten undertrykker melatoninniveauer, som igen sænker den anti-østrogene effekt af melatonin og ville således medføre en højere risiko for brystkræft. Der er utilstrækkelig dokumentation fra tidligere forskning til at implicere nat-skifteholdsarbejde i forhold til at forårsage brystkræft.

Objektivt: Vi udførte en systematisk gennemgang og meta-analyse for at vurdere styrken af sammenhængen mellem nat-skifteholdsarbejde eller tilbagevendende nat-skifteholdsarbejde og forekomsten af brystkræft.

Metoder: Flere databaser og ikke-elektroniske kilder blev systematisk søgt for at identificere case-kontrol og gruppeundersøgelser af kvinder i nat-skifteholdsarbejde. Sammenligningen var ikke-skifteholdsarbejde eller dagarbejde og resultatet indikerede brystkræft. Vi forholdt os til risikoen for partiskhed i studierne ved hjælp af en specifikt målrettet tjekliste på 10 interesse områder. Vi udførte meta-analyser med tilfældig virkning og meta-regressionsanalyse af studie-specifikke gradvise, relative risici for at bestemme risikoen for kræft forbundet med en 5 årig- og 300 natholds stigning i eksponering.

Resultat: Vi inkluderede 16 studier (12 case-kontrol og fire grupper). Ingen af undersøgelserne var i lav risiko for partiskhed. Meta-regression med tilfældige virkninger af dosisrespons, estimeret ved minimering af kvadratfejlsummen fra 12 undersøgelser viste, at nat-skifteholdsarbejde i over 5 år medfører en lille væsentlig trinvis risikostigning i case-kontrol studier. (RR1.09, 95% CI 1,02 til 1,2)i ikke gruppeundersøgelser (RR 1,01; 95% CI 0,97 til 1,05). Risiko med 300 nat-skift var 1,04 (95% CI 1 -1,10).

Følsomhedsanalyse med fast effekt model, forskellige dosis-respons modeller eller kun omfattende bedre kvalitet studier ændrede ikke disse resultater. Baseret på Dansk Selskab for Arbejds- og Miljømedicin's tilgang, var styrken af beviserne utilstrækkelige for tilstedeværelse eller fravær af kausalitet.

Konklusion: Beviserne fra 16 epidemiologiske undersøgelser, er utilstrækkelige til at dokumentere nat-skifteholdsarbejde øger risikoen for brystkræft. Bedre eksponeringsvurdering i fremtidige undersøgelser er nødvendig.

Contents

1. Background

Breast cancer

With almost 1.4 million cases in 2008, breast cancer is responsible for 23% of the total cancer cases and 14% of the cancer deaths across the world.

Breast cancer incidence increased in many Western countries in the late 1980s and 1990. However, incidence rates have decreased since 2000 in these countries supposedly due to lower use of combined postmenopausal hormone therapy which was prevalent previously. Breast cancer death rates have also decreased in these countries as a result of early detection and improved treatment (Jemal et al. 2011).

Breast cancer requires multidisciplinary management comprised of a chain of general and specialized care. This covers the entire process from detection, formal diagnosis, and treatment to follow up. Many sequential steps are involved in the diagnosis of breast cancer (clinical exam, scans, and lab tests) but a confirmed diagnosis is only possible with tissue histology of a biopsy specimen. Thus in epidemiological study of breast cancer histological confirmation is the method of diagnosis. Proxy measures such as mortality, morbidity, severity (grade or stage), or outcomes such as hormone levels (estrogen, melatonin) cannot be considered equivalent to the incidence of breast cancer itself. Similarly, benign breast diseases are also distinct from Breast cancer and should not be included with it.

Risk factors for Breast cancer

Like most other diseases, age is an important risk factor for breast cancer. The risk increases with increasing age becoming 1 in 37at 50-59 yrs and 1 in 26 between 60-69 yrs of age (American Cancer Society 2005).

Breast cancer incidence varies by ethnicity. It is lower for Asian females than Whites in the UK (Cancer Research UK 2011) and in the US (American Cancer Society 2005). Age adjusted US data shows that White women had the highest incidence rate (121/100,000) for breast cancer compared to 83/100,000 in Asian women (83/100,000) (Centers for Disease Control and Prevention 2012). The differences in genetic characteristics, age and maternity of the European and non-European/Asian populations may easily explain differences in breast cancer risks.

Breast cancer risk increases with higher social status, even when adjusted for ethnicity (Yost et al. 2001; Pudrovska et al. 2012). Breast cancer rates are also higher in high-income countries such as Western Europe, Australia and USA (World Health Organization 2012). This can be explained by lifestyle factors such as late first pregnancy, higher use of hormones (HRT/OC) and lower parity, along with better access to detection and treatment in affluent countries (Jemal et al. 2011).

Age at menarche, age at first birth, age at menopause, parity, use of HRT/OC, high estrogens and prolactin levels, previous breast disease and family history of breast cancer are known *reproductive* risk factors for breast cancers as reported in systematic reviews and meta-analyses of observational studies (Ewertz et al. 1990; Collaborative Group on Hormonal Factors in Breast Cancer 2001; Kahlenborn et al. 2006).

The known *life-style* risk factors for breast cancer include a greater body weight, a high BMI, alcohol intake low physical activity, high fat intake, and smoking, in order of relevance (Renehan et al. ; Khuder et al. 2001; Hamajima et al. 2002; Key et al. 2006; Turner 2011).

The exposure under study – Night-shift work

It is estimated that only a quarter of the working population are engaged in regular day work (Harma et al. 2010). Night work is carried out by 19% of the European working population and ten percent of them work nights more than five times a month. (European Foundation for the Improvement of Living and Working Conditions 2012). Around 7% of shift workers work permanently at night (Costa 2003).

Men are more often in night work than women but more women do permanent night-shifts than men (Costa 2003; European Foundation for the Improvement of Living and Working Conditions 2012). Most women in night work are younger than 25 years (European Foundation for the Improvement of Living and Working Conditions 2012).

In Europe night-shift work is most common in healthcare sector (35.5%) followed by plant and machine operators (34.5%) and hotel and restaurants (30%). In the USA, the highest prevalence is in leisure and hospitality industry (45.8%) followed by transport and utilities (27.8%) whereas the health and education industry has a much smaller 12.8% in shift work. Shift work is significantly more prevalent in African Americans than any other ethnicity and least prevalent in whites in the USA (IARC 2010).

Definition of the exposure

The International Agency for Research on Cancer (IARC) acknowledged in its monograph on carcinogenicity of shift work that night-shift work can be defined differently across the world. It states: the definition of

"period of night work" varies from country to country, i.e. in some countries it ranges from 8, 9 or 10 pm to 5, 6 or 7 am, and in many others from 11 or 12 pm to 5 or 6 am (European Foundation for the Improvement of Living and Working Conditions 2012).

An IARC working group that convened on consideration of shift work exposure in cancer studies considered night work or non-day shift work as "at least 3 hours of work between midnight and 05:00" (Stevens et al. 2010). The European foundation for working conditions considered night work as at least 2 hours of work between 22:00 and 05:00 (European Foundation for the Improvement of Living and Working Conditions 2012).

Measurement of the exposure

Shift work involving circadian disruption has been labeled a potential carcinogen by the IARC (IARC 2010). The decision was largely based on strong animal evidence whereas epidemiological evidence was considered weak. Their working group on shiftwork also argued that the estimation shift work exposure in epidemiological studies needs improvement before it can be considered comprehensive (Stevens et al. 2010). Following major domains were specified in particular and their use recommended in future research: Shift system, duration in years on a particular non-day shift schedule and cumulative exposure to the shifts over the subject's working life, and shift intensity (indicative of time off between successive work shifts).

How the exposure would lead to cancer

As many as five various, and often interlinked, mechanisms have been described in literature with at least some evidence of a biological plausibility for shift work causing breast cancer (Fritschi et al. 2011). The most researched of these in both animal models and epidemiological studies is the circadian disruption in night workers which apparently causes a mismatch between the body's circadian timing system and the environmental synchronizers (the light/dark cycle in particular), with consequent disturbances of the normal circadian rhythms of the body (Costa 2003). Circadian disruption can favour growth of malignant tumours in many ways. It is hypothesized that light at night suppresses melatonin levels (Gooley et al. 2011), which in turn lowers the anti-estrogen effect of melatonin (del Rio et al. 2004) and potentially increases the risk of breast cancer. Additional factors favouring tumour growth are potential defects in the regulation of the circadian cell cycle that occur in response to circadian disruption favouring uncontrolled growth. Moreover, sleep deprivation can lead to the suppression of immune surveillance that may permit the establishment of malignant clones (Costa et al. 2010).

Previous work

Three previous systematic reviews of the link between breast cancer and shift work have been published to date (Megdal 2005, Kolstad 2008, Erren 2008). We built on these reviews by expanding these with a systematic comprehensive search for and an extensive quality assessment of included studies.

In addition to these systematic reviews, in 2010 the IARC published a monograph on shift work and its causal association with cancer. A section in this expert overview pertained to breast cancer. The IARC expert group found strong animal data to support a causative link of night work with cancer however from eight epidemiologic studies (2 prospective cohort studies, and 6 case-control) and one meta-analysis it was concluded that the epidemiological evidence in humans was weak. The expert group concluded that shift work was probably carcinogenic for cancer in general and for breast cancer in women, especially in airline cabin crew (IARC 2010).

The insufficient reliability of the three previous systematic reviews for link between breast cancer and shift work indicated that a new methodologically rigorous review was needed.

In light of the existing evidence, a new systematic review to assess the association of shift work and breast cancer, sponsored by the Danish Work and Environment Fund, the findings of which are presented below.

We made a protocol for the systematic review available in the public domain on PROSPERO before the study selection began (Ijaz et al. 2012)

Objective

- To assess the magnitude (strength) of association between exposure to night-shift work or recurring night-shifts and incidence of breast cancer.

2. Methods

Criteria for considering studies

Study designs

We included prospective and retrospective cohort studies and case-control studies assessing the relationship between shift work and breast cancer.

We excluded cross sectional and case series studies or studies of cohorts that assessed incidence of a disease in a group of people without differentiating between exposed (to shift work) and non-exposed members.

Type of Participants

Working women.

We excluded female flight attendants, pilots or other airline crew because of the mixture of exposure to cosmic radiation and time zone changes with night-shift work that would be impossible to disentangle in epidemiological research. Therefore, it would not be possible to ascribe the results to exposure to night-shift work alone.

Type of Exposure

There is no universally accepted definition of night-shift work. Therefore in an attempt to be inclusive, in this review, any definition of night-shift work was acceptable as long as it included at least some work hours between 8 pm and 6 am.

Type of comparison

We included studies comparing any type of night-shift work as defined above versus day work or studies comparing various levels of exposure to shift work.

Type of Outcome measures

We only included studies where breast cancer was confirmed by histopathology for at least 90% of the cases.

We excluded mortality studies, and studies reporting benign breast disease, intermediate or secondary outcomes only.

Search methods

We searched Medline, EMBASE, CINAHL, Psyc Info, LILACS and OSH Update. Based on the concepts 'shift work' and 'breast cancer' we developed a search strategy for Medline via PubMed and adapted it to various databases (appendix A). Unlike randomized controlled trials, for which a sensitive and specific search filter is available, no reliable filter is available for comparative observational studies. We therefore did not include a filter for study design in our search to capture both case-control and cohort studies.

We checked the references from included studies and existing systematic reviews and the many available expert commentaries that have followed these reviews. We contacted subject experts and all authors of included studies with a request for information on any unpublished studies.

Selection of studies

An inclusion criteria template was developed and pilot tested specific to the research question (appendix B-1). Each title and abstract identified from the search was independently checked by two reviewers on the inclusion criteria. All review authors were involved in assessment. Discussion or a third reviewer (JV) resolved disagreement or ambiguity. Personal communication with the author(s) was used for obtaining additional information regarding inclusion.

Data extraction and management

Two reviewers extracted data from ach study independently on a standardized pre-piloted form (appendix B-2). Discussion or a third reviewer (JV) resolved any disagreement. Personal communication with the author(s) was attempted for obtaining additional information. Data on ‘night’ or ‘over-night work’ were chosen over evening or early morning only work. When no distinctions were made in the study we assumed the first choice. We chose self-reported exposure over that assessed by a job exposure matrix (JEM) alone when both were reported separately in a study.

Exposure modeling

The primary studies provided breast cancer risks for exposure to night shift work categories that varied widely between studies. Therefore we had to transform these into risk per comparable unit of exposure. To this end we calculated incremental relative risks per year of exposure to night-shift work on the one hand

and to life-time night-shifts on the other hand for each study. To make these breast cancer risks easier to interpret, we present the results for a relevant dose unit of 5 years exposure or 300 life-time night shifts. We considered the 5 years of night-shift work as an appropriate minimum increment to show change in risk based on the relatively small risk per year seen in two primary studies (Hansen 2011 and Davis 2001). Recent studies have been increasingly reporting risks for life-time number of shifts. This measure takes into account intensity of night-shift as well as duration. However the underlying assumption here is that the impact of the total number of shifts is the same whether they occur over one year or 5 years. We used a life time number of 300 night-shifts as a minimum incremental step, representing one year of permanent/fixed night work. The European working time directive on night-shift allows for a maximum of six 12 hour shifts a week. Work schedules vary across locations but four 12 hour shifts or six eight hour shifts per week are the commonest. This makes for a maximum of approximately 300 eight hour shifts that can occur in a year of permanent night work.

To enable the calculation of study specific incremental relative risks, we first assigned a single dose to each night-shift work exposure category reported in a study: for closed categories we assigned the midpoint and for highest open categories we used a dose based on the lower bound of the open category plus the range of the second highest category (Il'yasova et al. 2005). For five studies where we got information from authors we used doses as advised for open ended highest categories which were always close to the lower boundary of the open category. With these dose-risk data, we estimated incremental relative risks or trends per study with the generalized least squares for trend estimation method (GLST) as described by (Orsini et al. 2006) and (Greenland et al. 2008). (Table 3)

All studies reporting years of night-shift work in at least two categories were included in the 5 year incremental risk meta-analysis. When life-time shifts or an average intensity (number of shifts per month) was available for exposure categories or for the entire study sample the study was included in the 300 shift incremental increase analysis.

Assessment of risk of bias in included studies

We assessed the risk of bias in the included studies according to the recommended methods of systematic reviews as part of data extraction: in-duplicate, independently for each study and consensus achieved for each rating.

We assessed each included study against ten important bias domains for the question under study. We adapted the risk of bias checklist for our review from a validated checklist for observational studies of incidence (Shamliyan et al. 2010a; Shamliyan et al. 2010b). We considered the domains into two hierarchical groups:

- 1st group: Exposure definition, Exposure assessments, Reliability of assessments, Confounding, Analysis methods in the study (Research Specific Bias)
- 2nd group: Blinding of assessors, Attrition, Selective reporting, Funding and Conflict of interest

We categorized each domain as either at high (poor methods to avoid bias), low (best practice) or unclear (poor reporting/insufficient information) risk of bias. Our cut-off points for high and low risks of bias in each domain were content specific to our research question and finalized by consensus of the research team. We then rated the risk of bias in each study as a whole as follows:

- low risk of bias: low risk in all 5 domains of the 1st group and at least 2 of the domains from the second group.
- moderate risk of bias: low risk of bias in at least 4 domains in 1st group and 2 domains in second group.
- high risk: less than 4 domains from first group at low risk of bias

The detailed criteria at domain and study level along with the adapted checklist are available in appendix B-2.

Measures of effects

Relative risks (RR) for cohort studies and odds ratios (OR) for case-control studies were extracted for categories of years of exposure and categories of life-time shifts. Given the low incidence of breast cancer we considered the values of RRs and ORs equivalent (Cummings 2009).

Adjustment for confounding

We wanted to define a set of factors that are consistently associated with shift workers and are established risk factors for breast cancer. We used a directed acyclic graph (DAG) to visualize the degree of bias for the effect estimate (Shrier et al. 2008), created with DAGitty (Textor 2011) (http://www.dagitty.net/) (see Appendix C for details). This helped us decide on the following confounder set for the association of night-shift work with breast cancer: Age, Ethnicity, Socioeconomic status, Parity (number of children, age at first child), and BMI (overweight, obese).

We had planned to adjust the effect estimates following the methods described by Greenland if studies had not adjusted for any of these listed confounders (Greenland et al. 2008). We obtained information from many relevant authors eliminating the need for adjusting ourselves as much as possible. For one study where we had enough data available and could do the adjustment based on available data, it did not change the results.

Data synthesis

We transformed the exposure categories reported in each study into a dose and then obtained incremental risk estimates (table 3) We performed a two stage random effects GLST meta-analysis, based on the best fitting model, to model the pooled incremental risk estimate overall and for case-control and cohorts separately (Orsini et al 2012, Greenland et al. 2008). We used STATA XII for the analyses. This dose response meta-analysis based on generalized least squares regression takes into account the correlation of risk per dose category because they all use a zero dose as the reference within a study.

Assessment of heterogeneity

Studies of different design were analysed in subgroups. We assessed statistical heterogeneity by means of the I^2 statistic (Higgins et al. 2002; Higgins et al. 2003). We took the values of I^2 of 25%, 50% and 75% as low, moderate and high degrees of heterogeneity respectively.

Investigation of heterogeneity

We pre-specified factors that can modify effect of shift work on breast cancer risk. We performed a random effects meta-regression analysis in STATA IX (StataCorp 2005) to evaluate these study-level factors:

- Types of occupation- where we took health care shift workers as one occupation versus shift workers in other industries;

- Tite of the study - studies that are carried out in high income countries (according to the IMF definition) and those from low and middle income countries; and
- Type of shift system - rotating shifts vs fixed shifts or fixed and rotating mixed together.

Sensitivity analysis

We performed a fixed effect analysis to test our model assumptions.
We performed sensitivity analyses to check sensitivity of our results to the inclusion of low quality studies. Additional to these a priori analyses we tested the options used for calculating the dose. We capped the 20+ years highest open ended exposure categories by using the value of the lowest bound of the highest open category as the dose value. In addition, we tested the assumptions underlying the dose-response relationship by fitting a cubic spline model with various knots and a log function using the natural logarithm of the dose for the exposure. We tested if this improved the goodness of fit of the fitted models.

Assessment of reporting biases

We tried to avoid reporting biases by including studies in any language and by searching for unpublished studies and data. We assessed publication bias formally by observing funnel plot asymmetry and performing the Egger's test to ascertain bias due to small studies (Egger et al. 1997).

Grading/ Strength of the evidence on causality

We used the approach of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine to grade the degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome - Appendix D.

In addition, we used the GRADE approach to assess the overall quality of evidence - Appendix E. The criteria for downgrading used in GRADE approach are: indirectness, inconsistency, risk of bias, publication bias, and imprecision. For upgrading GRADE uses: a big effect size, a very big effect size, all confounders would work towards the nil, spurious factors would work towards the nil.

3.

3. Results

Search results

We found 6728 records from database searches and four records were through reference searching of included articles. We assessed title and abstracts of 5336 records after duplicate removal. Fifty seven full text reports were sought for further assessment of which five were in languages other than English (Three German, one French, and one Chinese). Twenty seven studies were excluded. These are tabulated with reasons in the table of Excluded studies (Appendix F).

Three articles describe ongoing studies and two are still awaiting classification because full text reports of study could not be obtained (see table of studies ongoing or awaiting classification Appendix G). These should be included in the update of the review.

Sixteen studies based on 25 reports have been included in the review and 12 in the meta-analysis of exposure duration and 8 in the number of cumulative night-shifts. See Fig. 1 for flow of studies diagram:

The details of all included studies are presented in the Characteristics of included studies tables 1 a, 1 b and 1 c.

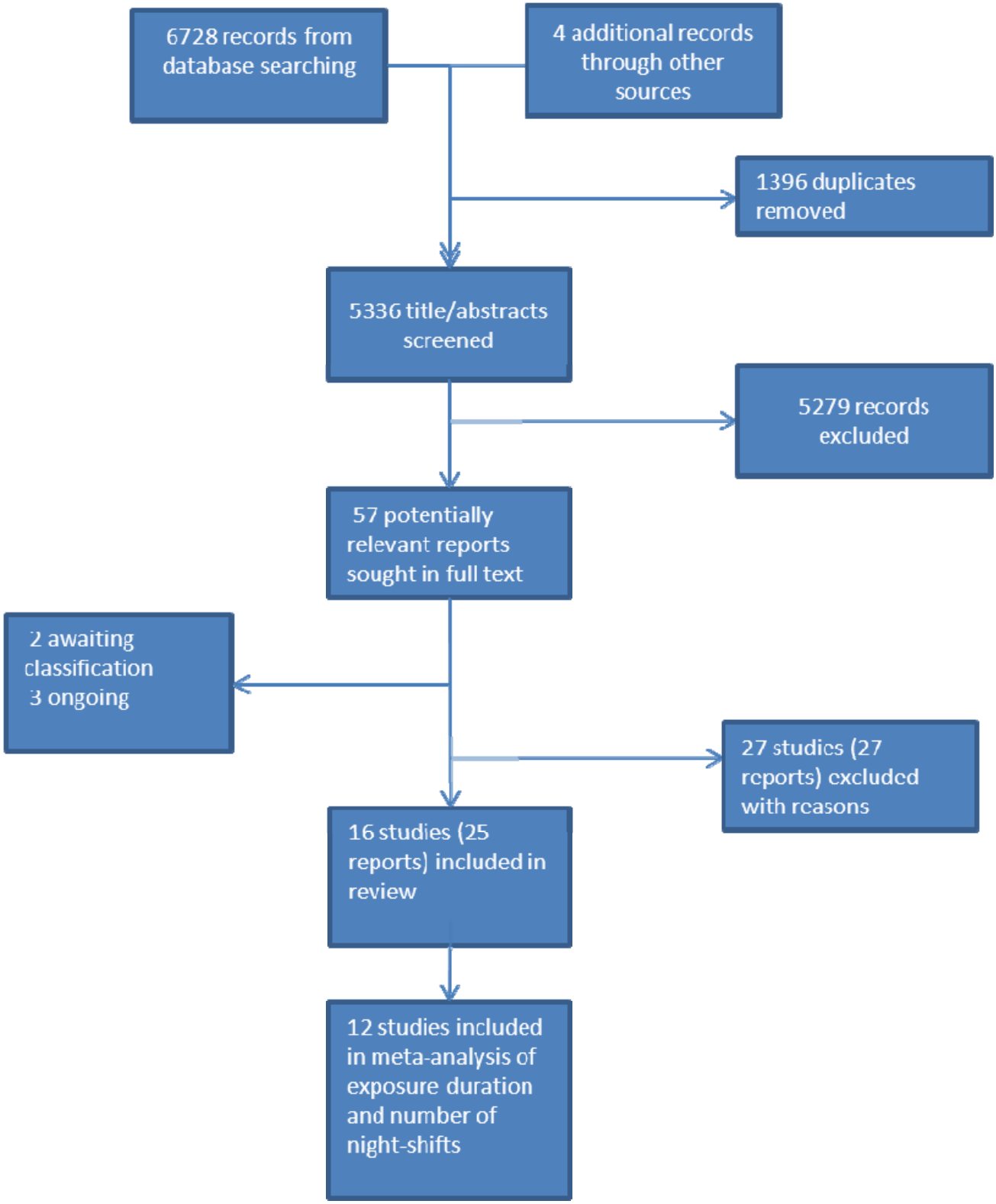


Figure 1: Study Flow Diagram

Description of studies

Included studies

Study design

Four of the 16 studies were prospective cohort studies (Schernhammer et al. 2001;Schernhammer et al. 2006;Pronk et al. 2010;Knutsson et al. 2012) where participants were followed for 12, 10, 9 and 12.4 years respectively. Eleven studies were retrospective, including five nested case-controls studies (Tynes et al. 1996; Lie et al. 2006; Hansen et al. 2011; Lie et al. 2011; Hansen et al. 2012), one nested case cohort study (Li 2011) and three population-based case-control studies (O'Leary et al. 2006; Pesch et al. 2010; Menegaux et al. 2012).

Study size

Study size ranged from 309 to 113,216 participants with a mean of 25,747. Altogether 16,519 cases of breast cancer were analysed in 16 studies.

Geographical Location

Four studies were conducted in USA, three each in Norway and Denmark, two in Sweden, two in China and one each in France and Germany. The oldest study started in 1976 (year of baseline exam for cohort) and the most recent in 2009.

Participants

All studies involved females only, except Schwartzbaum 2007 who report for all cancers separately in men and women. Sources of participants varied among studies with seven out of 16 identifying participants from administrative and/or cancer registries. Four studies recruited participants from the general population (O'Leary 2006, Pesch 2010, Pronk 2010, Menegaux 2012) and the remaining five recruited participants from established occupational cohorts (Schernhammer 2001, Schernhammer 2006, Tynes 1996, Knutsson 2012, Li 2011).

Participants ranged in age from 20 to 85 years. Mean age for the sample was reported infrequently, in only four studies. Most studies reported age categories with number of participants in each.

Nurses were the most commonly studied occupational group with five studies addressing nurses. One study focused on radio and telegraph operators, one on military personnel and one on textile factory workers. One reported studying a group of occupations (Manufacture of beverages, land transport services, catering

and air transport services). The remaining six did not specify an occupation and likely studied various. Details of studies can be seen in tables 1-a, b and c.

Exposure: Nomenclature

Eight studies used the terms ‘night work’ or ‘night-shift work’ to describe exposure. However, various similar names (shift work, over-night-shift, rotating night work, permanent night work, graveyard shift, working outside day time hours, and trades with night work) were reported indicating the aspects of night-shift work important to the researchers.

Exposure: Defining shift work

Definitions of shift work improved in recent years incorporating more IARC advised concepts.

Definitions usually included start and end times for night-shifts (10 studies). These times ranged from start of shift as early as 7pm or as late at 12pm and finishing shift as early as 4am and as late as 9am. Four studies considered shift system as part of the exposure definition. One of them included only rotating shifts, one differentiated between permanent and rotating shifts, while the other two did not. Duration of at least six months was the minimum consideration for exposure in two studies and three used one year as minimum for exposure. Frequency of shifts per week or per month was part of the definition in five studies.

Table 1-a Characteristics of included studies

Study ID Author, pub.year	*Study design*	*Sources of participants*	*Number of participants (analysed)*	*Mean age years*	*Occupation*	*Location*	*Exposure: Source of information*
Davis 2001	Population-based Case-control	Cases: population-based cancer registries; Control: population random-digit dialing	Total 1 510. Cases: 767 Controls: 741	47	Various	USA	Interviews
Hansen 2001	Nested Case-control	Danish Nurses Association; cases linked to Danish Cancer Registry,	Total 12 305. Cases: 6281 Controls: 6024	42	Various	Denmark	Employment histories from files of pension fund
Hansen 2011	Nested Case-control	Danish Nurses Association; cases linked to Danish Cancer Registry	Total 1 302. Cases: 267 Controls: 1035	< 70	Nursing	Denmark	Interviews
Hansen 2012	Nested Case-control	Danish military; cases linked to Danish Cancer Registry	Total 637. Cases: 132 Controls: 505	< 70	Military	Denmark	Questionnaires / interviews
Knutsson 2012	Cohort, Prospective	Women in the WOLF (Work, Lipids, and Fibrinogen) cohort; cases linked to	Total 3 060. Exposed: 549. Controls: 2 511	41	Various	Sweden	Questionnaires
Li 2011	Nested Case-control	Textile factories of the Shanghai Textile Industry Bureau (STIB) ; cases linked to	Total 6 489. Cases: 1 709 Controls: 4 780	48	Textile industry	China	Factory personnel records, interviews
Lie 2006	Nested Case-control	Norwegian Board of Health's registry of nurses; cases linked to	Total 2 680. Cases: 537 Controls: 2 143	27 – 85	Nursing	Norway	Norwegian Board of Health's registry of nurses
Lie 2011	Nested Case-control	Norwegian Board of Health's registry of nurses; cases linked to	Total 1 594. Cases: 699 Controls: 895	54.5	Nursing	Norway	Interviews
Menegaux 2011	Population-based Case-control	Hospitals in two French departments	Total 2 549. Cases:1 232 Controls:1 317	49	Various	France	Interviews
O'Leary 2006	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 2010	Population-based Case-control	Women from the Greater Region of Bonn, Germany (GENICA Study)	Total 1 539. Cases: 746 Controls: 793	56	Various	Germany	Interviews

Pronk 2010	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 JEM
Schernhammer 2001	Cohort, Prospective	Female registered nurses enrolled in the Nurses' Health Study.	Total 78 562. Exposed 46 801 Unexposed 31 761 Cases: 2 441	55	Nurses	USA	Questionnaires
Schernhammer 2006	Cohort, Prospective	Female registered nurses enrolled in the Nurses' Health Study II.	Total 11 3216. Exposed: 78 063 Unexposed: 35 153. Cases: 1 352	40	Nurses	USA	Questionnaires
Schwartzbaum 2007	Cohort, Retrospective	Randomly samp of gainfully employed people in 1960 and 1970 population censuses	Total 1 148. 661. Exposed: 3 057 Unexposed:1 145 604 Cases: 98	57	Various	Sweden	Census and Annual Survey of Living Conditions
Tynes 1996	Nested Case-control	Norwegian Telecom cohort	Total 309. Cases: 50 Controls: 259	52	Radio/telegraph operator	Norway	Norwegian seamen registry

Table 1 b Characteristic of included studies- Exposure

Study ID	*Shift work description*	*Exposure definition*	*Reference category definition*	*Exposure duration (mean, years)*	*Exposure intensity (mean shifts per month)*	*Shift system*
Davis 2001	Graveyard shift	Beginning work after 7:00pm and leaving work before 9:00am.	Zero years worked at least one graveyard shift per week	Cases: 4.5 Controls: 3.1	Not reported	Not reported
Hansen 2001	Trades in which at least 60% of the female responders worked at night	At least half a year in trades with predominantly (>60%) night work	Employed in trades with less than 40% night work.	Not reported	Not reported	Not reported
Hansen 2011	Working outside normal daytime hours, Nightshift work, Graveyard shift	Night-shift: from 11:00pm-12:00am to 7:00 – 8:00 am; Graveyard shift: about 8 hrs of work between 7:00pm and 9:00am for one year	Permanent day or day-evening work	Cases: 11.9 Controls: 10.9	Not reported	Rotating and fixed
Hansen 2012	Night shift work	Working at least 1 year during hours beginning after 5:00pm and ending before 9:00am; permanent and rotating night-shifts assessed as one	Women with <1 year of night work.	Not reported	Not reported	Rotating and fixed
Knutsson 2012	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: 6.00 - 18.00 hours	9.39 (SD) 9.53	Not reported	Backward rotating, forward rotating and fixed
Li 2011	Rotating night-shift work	Working continuously between 12:00pm and 5:00 am in a rotating shift schedule	Day work only, non-shift work only	Cases 12.9 yrs	Not reported. Calculated 8.6 nights per month	Rotating

Study ID	*Shift work description*	*Exposure definition*	*Reference category definition*	*Exposure duration (mean, years)*	*Exposure intensity (mean shifts per month)*	*Shift system*
Lie 2006	Night work	Nurses working at infirmaries	Managerial jobs, teaching, and work at physiotherapy or out-patients' departments.	Cases 16.7 Controls 15	Not reported	Not reported
Lie 2011	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 at least 12:00 pm until 6:00 am,	Nurses who never worked at night after graduation	75% of controls has less than 12 yrs exposure	Not reported.	Rotating and fixed
Menegaux 2011	Night work	Worked for at least 1 hr between 11:00 pm and 5:00 am. 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 11:00 pm – 5:00 am	Never worked at night	Controls 4.5 yrs median	Controls median 12 nights per month Cases Not reported	No assessment of shift systems
O'Leary 2006	Shift work, evening shift, overnight-shift	Overnight-shifts: could start as early as 7:00 pm and continue until the following morning	Never held jobs involving shift work	Not reported	Not reported	Not reported
Pesch 2010	Night-shift work	Work between 12:00am – 5:00 am	Day work only; ever employed never night work	Not reported	Not reported	Not reported
Pronk 2010	Night-shift work	Starting work after 10:00 pm at least 3 times a month for over 1 year.	Never did shift work	Not reported	Not reported	Not reported
Schernhammer 2001	Rotating night-shift work	Years in rotating night-shifts with at least three nights per month in addition to days or evenings.	Never worked on rotating night-shifts	Not reported. 1 - 30+ yrs	6.5 per month	Rotating

Study ID	*Shift work description*	*Exposure definition*	*Reference category definition*	*Exposure duration (mean, years)*	*Exposure intensity (mean shifts per month)*	*Shift system*
Schernhammer 2006	Rotating or permanent night work	Years worked rotating night-shifts with at least 3 nights per month in addition to days or evenings and/or years worked permanent night-shifts for 6 or more months	Never worked rotating or permanent night-shift	Not reported	6.5 per month	Rotating and fixed
Schwartzbaum 2007	Shift work	Workplace with a rotating schedule with 3 or more possible shifts per day or had work hours during the night (any hour between 1:00am and 4:00 am) at least 1 day during the week preceding the interview.	People in occupation–industry combinations in which less than 30% were shift workers.	Not reported	Not reported	Rotating and fixed
Tynes 1996	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

Exposure: defining non-shift work (reference group)

The most common definition used (7 studies) for the reference group was never night (or shift) work. Other definitions could be categorized into those by:

- job title or nature (working in trades with less than 30% or 40% people in shift work, never holding a job involving shift work, nurses working outside infirmaries, women in permanent day work, day evening rotation work),
- duration in shift work (0 years in shift work, less than 1 year in night work, less than 6 month in permanent night-shift)
- frequency of shift work (less than one per week evening or overnight work - in zero years of shift work)
- If data indicated day work on more than one occasion and no indication of shift work

Exposure: intensity and duration reported

Ten studies reported exposure as binary categorical data (yes vs. no shift work). Although a useful descriptor to understand how many people there were in shift or no shift work, it is not a very precise classification of exposure to shifts. This is especially so, when definition of the two groups is also categorical with an arbitrary threshold.

Duration of shift work in years was the most common descriptor for exposure data with 12 studies reporting categories of increasing years of exposure and two reporting increasing duration with increasing frequency categories.

Cumulative shift work exposure data were seen more in recent studies. Five studies reported cumulative life time number of shifts for various exposure levels.

Outcome

Included studies reported only breast cancer incidence with only one study (Schwartzbaum 2007) reporting other site specific cancers in men and women in addition to breast cancer in women. Intermediate lab outcomes or hormone levels were not reported in any study.

Confounders assessed

Of the five confounding factors considered for this review, age and parity were adjusted for most often (see table 1-c).

Age was adjusted for in all studies, and parity in all but one (Schwartzbaum 2007). Seven studies adjusted for socioeconomic status or a proxy (education) clearly and for one other study it was considered adequate based on data available for that cohort outside the study (Hansen 2011). Ethnicity was considered

adequately adjusted/matched or irrelevant in nine studies. BMI was adjusted for in eight studies. Six studies had adjusted for all these confounders.

Excluded studies

The studies were excluded mostly because no assessment of shift work was done (24). The other two reasons for exclusion were the absence of a reference no shift working group (7) and the outcome being mortality or morbidity instead of incident breast cancer (1).

Table 1 c Characteristics of included studies- effect measurement and confounder adjustment

Study ID	***RR per exposure vs no exposure***	***RR per exposure duration***	***RR per duration intensity exposure*** [1]	***Effect estimate***	***Adjusted for***				
					Age	***Parity***	***BMI***	***SES***	***Ethnicity***
Davis 2001	Yes	Yes	0	OR,IRR	Yes	Yes	No	No	No
Hansen 2001	Yes	No	0	OR	Yes	Yes	No	Yes	Yes
Hansen 2011	Yes	Yes	2	OR, IRR	Yes	Yes	Yes	Yes	Yes
Hansen 2012	Yes	Yes	1, 2	OR	Yes	Yes	Yes	Yes	Yes
Knutsson 2012	Yes	No	0	HR	Yes	Yes	Yes	Yes	Yes
Li 2011	No	Yes	2	HR	Yes	Yes	No	No	Yes
Lie 2006	No	Yes	0	OR	Yes	Yes	No	No	Yes
Lie 2011	No	Yes	1	OR	Yes	Yes	Yes	No	Yes
Menegaux 2011	Yes	Yes	1,2	OR	Yes	Yes	Yes	Yes	Yes
O'Leary 2006	Yes	Yes	1	OR	Yes	Yes	No	Yes	No
Pesch 2010	Yes	Yes	2	OR	Yes	Yes	Yes	Yes	Yes
Pronk 2010	Yes	Yes	1, 2	RR	Yes	Yes	Yes	Yes	Yes
Schernhammer 2001	No	Yes	3	RR	Yes	Yes	Yes	Yes	Yes
Schernhammer 2006	No	Yes	3	RR	Yes	Yes	Yes	Yes	Yes
Schwartzbaum 2007	Yes	No	0	SIR	Yes	No	No	Yes	Yes
Tynes 1996	No	No	1	OR	Yes	Yes	No	No	No

[1] *(0=no, 1=duration and intensity reported, 2= life time night-shifts reported, 3= intensity obtained from authors)*

Risk of bias in included studies

The risk of bias is presented in table 2. The complete risk of bias table for each included study with support for judgments is presented in Appendix H.

Exposure definition

Of the 16 studies included, six were deemed at low risk of bias in how they defined night-shift work as per pre-defined criteria (Pronk 2010, Lie 2011, Hansen 2011, Li 2011, Hansen 2012, Menegaux 2012) by incorporating two IARC advised components into the definition of shift work exposure, although none included all three.

The remaining 10 studies were marked at high risk of bias as the definitions did not include at least two components of shift work recommended by the IARC.

Exposure assessment

Only one study used objective exposure assessment from prospectively collected employer records (Li 2011) and was marked at low risk of bias in this domain.

All other included studies were at a high risk of bias in this domain, as they used subjective measures to assess exposure or categorized exposure based on occupation. Six studies used in person interviews for exposure assessment, three used job exposure matrix of some kind. Three employed posted questionnaires. Two studies (Hansen 2012, Menegaux 2012) used questionnaires along with in-person interviews. One study (Pronk 2010) used a job matrix developed specifically for the study and applied it in conjunction with self-report.

Confounding

Ten of the 16 studies were considered at low risk of bias for adjusting for four of the five major confounding factors for this review (Schernhammer 2001, Schernhammer 2006, Pesch 2010, Pronk 2010, Menegaux 2012, Knutsson 2012, Lie 2011, Hansen 2001, Hansen 2011, and Hansen 2012). Only one study (Menegaux 2012) matched controls on predefined categories of socioeconomic status (SES). Five studies were deemed to be at high risk in this domain for addressing less than four of the main confounding factors.

The only study with unclear risk in this domain is Li 2011 as clarification from authors could not be obtained before the submission of this report.

Analysis/research specific bias

For both case-control and cohort studies included in the analysis, methods used were valid and appropriate for the respective study design. One study used boot strapping for adjustment of the results (Pesch 2010) while the rest presented adjusted estimates.

Dose response was assessed appropriately in ten studies as either categories of increasing duration or frequency or both, although categories were of variable size. The one study at unclear risk (O'Leary 2006) is where contacts with authors could not be established to confirm analysis methods.

Based on pre specified criteria, ten studies were at low risk in this domain and five at high risk. All five (Tynes 1996, Davis 2001, Hansen 2001, Schwartzbaum 2007, Li 2011 and Knutsson 2012) at high risk were considered so because of a lack of dose response assessment to an adequate level in addition to no description of the considerations underlying the sample selection.

Reliability of exposure estimates

For thirteen studies the risk of bias in this domain was low because the reports clearly stated that same methods for assessment of exposure were used or reliability was tested or this could be confirmed with the authors. For the remaining three studies this could not be confirmed and these were marked unclear.

Blinding of assessors

Exposure was prospectively allocated in three cohorts and two nested case-control studies (Schernhammer 2001, 2006, Pronk 2010, Li 2011, Pesch 2010) and these were considered at low risk of bias. Assessors were blind to case status in two case-control studies (Hansen 2012, Lie 2011). Three case-control studies were at high risk (Menegaux 2012, Lie 2006, Tynes 1996). For the remaining studies enough information was not available to determine the risk of bias and these were marked unclear.

Attrition (loss of participants)

Nine studies were at low risk of bias in this domain including six case-control and three prospective cohort studies (Pronk 2010, Schernhammer 2001 and 2006). Remaining seven studies were at high risk of bias.

Selective reporting

Even though almost all studies (14) appear at low risk of bias for this domain, it should be noted that the lack of a protocol necessitated us using aims stated in the actual report (abstracts and methods) of the

study as a criteria to measure selective reporting. This may underestimate the selective reporting bias. The only two studies deemed at high risk were Tynes 1996 and Schwartzbaum 2007.

Funding and conflict of interest

No study was funded by a commercial organization. Fourteen were funded by noncommercial/public organizations, and two did not report any funding source (Tynes 1996, Hansen 2001). For 12 studies we could confirm from authors that sponsors had no role in conduct or reporting of the study thus marking these at low risk for funding bias. The rest remain at an unclear risk even though we acknowledge that the risk due to funding is likely low for these as well.

Thirteen studies had no conflict of interest as reported by authors either in reports or in communication with us.

Overall quality per study

Within these 16 studies none was at a low risk of bias according to predefined criteria because exposure assessments were ubiquitously at high risk, except in Li 2011.

Six studies were of moderate quality (studies with four domains of the first group and two of the second group at low risk). These were Hansen 2012, Hansen 2011, Li 2011, Lie 2011, Menegaux 2012, and Pronk 2010. Only Pronk 2010 was a prospective cohort design.

Table 2: Risk of Bias in and across included studies

Study ID	Davis 2001	Hansen 2001	Hansen 2011	Hansen 2012	Knutsson 2012	Li 2011	Lie 2006	Lie 2011	Menegaux 2012	O'Leary 2006	Pesch 2010	Pronk 2010
Exposure definition	High risk	High risk	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk	High risk	High risk	Low risk
Exposure assessment	High risk	High risk	High risk	High risk	High risk	Low risk	High risk	High risk	High risk	High risk	High risk	High risk
Reliability of exposure estimates	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Analysis/research specific bias	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk
Confounding	High risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk
Attrition	High risk	Low risk	High risk	High risk	High risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	Low risk
Blinding of assessors	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	High risk	Low risk	High risk	Unclear risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Funding	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk
Conflict of interest	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Effects of exposure

The categories of exposures were converted into doses and reported risk estimates for the various categories were converted into 5 year and 300 shift estimates which are presented in table 3.

Table 3: Exposure categories and their respective calculated doses, reported and transformed risk estimates from studies included in meta-analysis

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
Davis 2001 years	Ref	1	0	1.13(1.01-1.27)	1.88 (0.82- 4.3)	Not estimable
	1-2	1.4 (0.6-3.2)	1.5			
	3+	1.6 (0.8-3.2)	4			
Hansen 2011 years	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			
	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 2011 number of shifts	Ref	1	0			
	1-467	1.6 (1.0–2.6)	434			
	468-1095	2.0 (1.3–3.0)	781.1			
	1096+	2.2 (1.5–3.2)	1722			
Hansen 2012 years	Ref	1	0	Not reported	1.15 (0.99-1.33)	1.10 (1.02-1.18)
	1-5.9	0.9 (0.4 to 1.7)	3.45			
	6-14.9	1.6 (0.9 to 3.2)	10.45			
	15+	1.8 (1.0 to 4.5)	23.9			
Hansen 2012 number of shifts	Ref	1	0			
	1-415	0.8 (0.4-1.9)	208			
	416-1560	1.4 (0.7-2.9)	988			
	1561+	2.3 (1.2-4.6)	2705			
Lie 2006 years	Ref	1	0	Not reported	1.12 (1.03-1.20)	Not estimable
	1-14	0.95 (0.67–1.33)	7.5			
	15-29	1.29 (0.82–2.02)	21.5			
	30+	2.21 (1.10–4.45)	36			
Lie 2011years	Ref	1	0	Not reported	1.04 (0.97-1.14)	1.02 (0.98-1.07)
	1-11	1.2 (0.9-1.5)	6			
	12+	1.3 (0.9-1.8)	19.9			
Lie 2011 number of	Ref	1	0			

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
shifts	<1006	1.2 (0.9, 1.6)	503.5			
	1007+	1.2 (0.9-1.7)	2012			
Menegaux 2012 years	Ref	1	0	Not reported	1.21 (1.01-1.45)	1.03 (0.96-1.1)
	0.03-4.4	1.27 (0.83–1.94)	2.2			
	4.5+	1.40 (0.96–2.04)	8.9			
Menegaux 2012 shifts	Ref	1	0	Not reported		
	1-663	0.92 (0.45–1.89)	332			
	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 2006 years	Ref	1	0	Not reported	0.66 (0.48-0.93)	Not estimable
	1-7	0.74(0.32, 1.68)	4			
	8+	0.32 (0.12, 0.83)	14			
Pronk 2010 years	Ref	1	0	Not reported	0.96 (0.89-1.03)	0.97 (0.92-1.02)
	1-5	0.9 (0.6-1.3)	3			
	6-17	0.9 (0.6-1.4)	11.5			
	18+	0.8 (0.5-1.2)	29			
Pronk 2010 number of shifts	Ref	1	0			
	1-579	0.9 (0.6 -1.3)	288.5			
	577-1632	1 (0.7-1.5)	1104.5			
	1633+	0.7 (0.4 -1.1)	2688			
Pesch 2010 years	Ref	1	0	Not reported	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 2010 number of shifts	Ref	1	0			
	1-807	0.65 (0.34–1.26)	404			
	808+	1.73 (0.71–4.22)	1614			
Schernhammer 2001 years	Ref	1	0	Not reported	1.04 (1- 1.07)	1.03 (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			

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
Schernhammer 2001 number of shifts @6.5nights per month	Ref	1	0			
	78-1092	Not reported	585			
	1170-2262	Not reported	1716			
	2340+	Not reported	2340			
Schernhammer 2006	Ref	1	0	Not reported	1.01 (0.94-1.08)	1.01 (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 2006 number of shifts@6.5nights per month	Ref	1	0			
	78-702	Not reported	390			
	780-1482	Not reported	1131			
	1560+	Not reported	1560			
Tynes 1999 years	Ref	1	0	Not reported	1.40 (0.75- 2.6)	Not estimable
	0.1-3.1	0.3 (0.1-1.2)	1.6			
	3.2+	0.9 (0.3-2.9)	11.9			

Risk per 5 year exposure to night-shift work

The meta-analysis of 12 studies showed a small significant relative risk increase for working at night for 5 years (RR 1.05, 95% CI 1.01 - 1.10), Figure 1. Heterogeneity was moderate (I^2 =55%) The relative risk in cohort studies alone was non-significant with a RR of 1.01 (95% CI 0.97 - 1.05) and little heterogeneity with I^2 of 34% and for case-control studies the RR was 1.09 (95% CI 1.02 - 1.2) with I^2 of 45%.

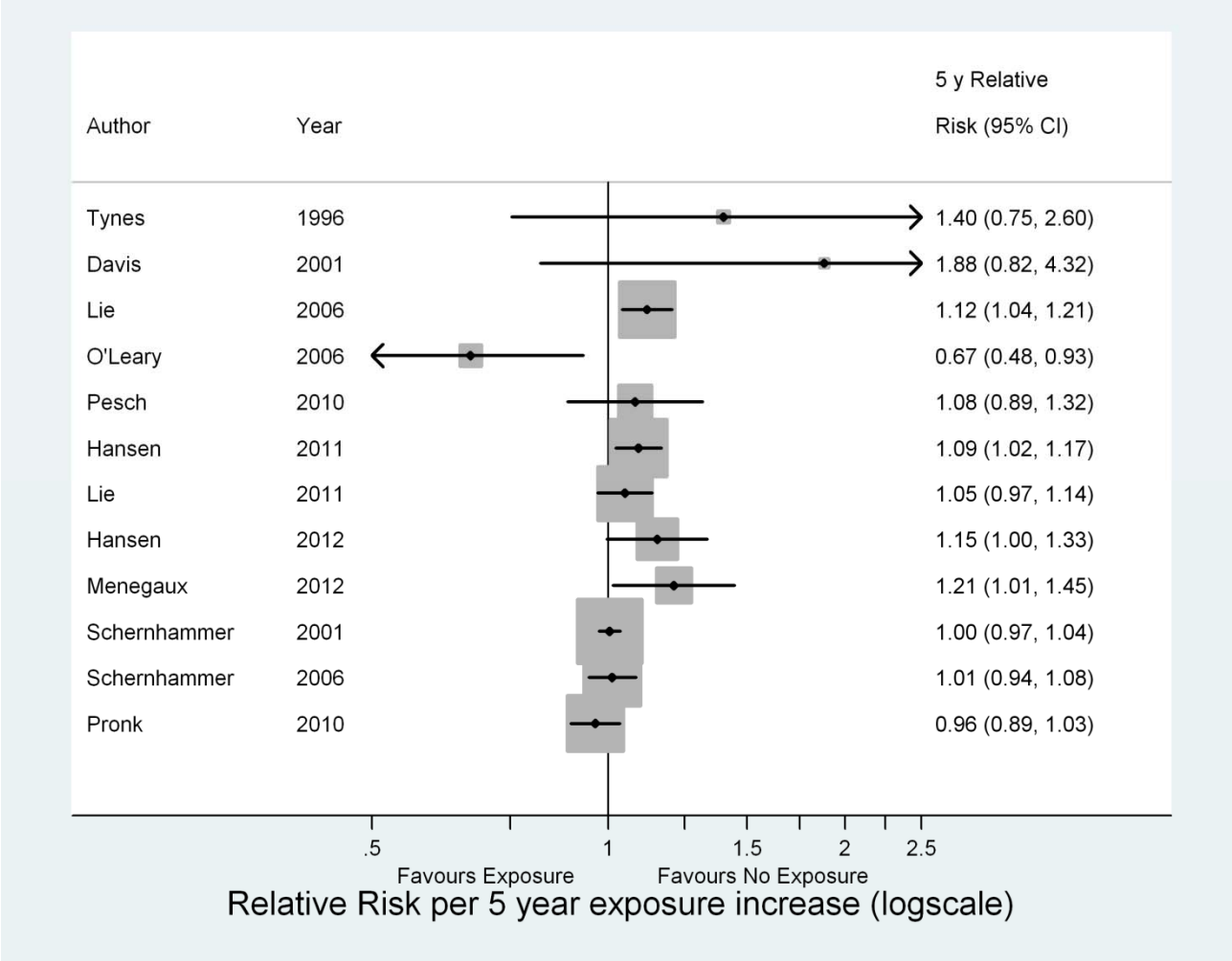


Figure 1: Random effects dose response meta-analysis of 12 included studies - risk for 5 years of night-shift

Risk per 300 cumulative night-shifts

The meta-analysis of eight studies indicated a similar small, significant association of 300 night shifts with breast cancer (RR 1.04, 95% CI 1.0 - 1.1) Figure 2. Heterogeneity among studies was moderate (I^2= 58%). The relative risk for cohort studies was 1.0 (95% CI 0.97 to 1.04) with I^2 of 53% and for case-control studies was 1.07 (95% CI 1.00 - 1.10) with I^2 of 37 %.

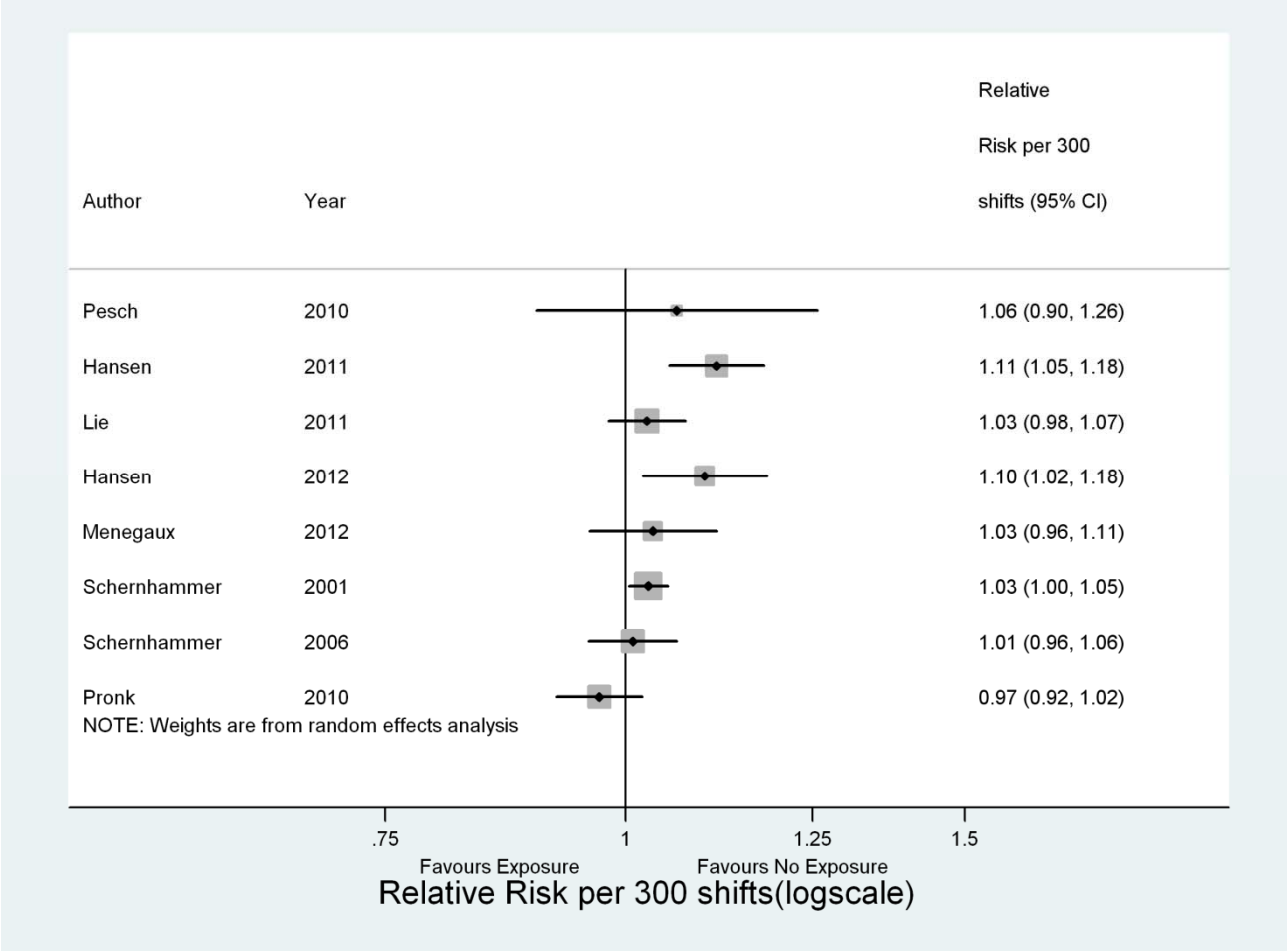


Figure 2: Random effects dose response meta-analysis of 8 studies - risk for 300 night-shifts

Effects of studies that could not be included in the meta-analysis

Four studies could not be included in our meta-analysis as data were not amenable to modeling of exposure. Three of these were cohort studies (Schwarzbaum 2007, Li 2011, Kuntsson 2012) and one a case control (Hansen 2001). Two report risk for being in an occupation where shift work is prevalent (Schwartzbaum 2007, Hansen 2001). One provides estimates for being in shift work as reported by participants on at least two occasions (Knutson 2012). None of these provided risks for a duration in years exposure, which was essential for calculating risks per 5 years. For one study (Li 2011) we did not have information on number of controls for the various categories to allow entering it into the model until the submission of this report.

The risk estimates provided in these studies were:

Hansen 2001: OR 1.50 (95% CI 1.30 to 1.73) for women who had worked for at least half a year in trades with predominantly (>60%) night work compared to trades with less than 40% night work,

Knutsson 2012: HR 2.02 (95% CI 1.03 to 3.9) for shift work with night work on ≥1 measurement occasion compared to day work on all occasions.

Li 2011: HR 0.94 (95 % CI 0.72 to 1.22) for rotating night work for over 20 years compared to only day work.

Schwartzbaum 2007: SIR 0.97 (95% CI 0.67 to 1.40) in those marked shift workers in both 1960 and 1970 census.

The potential effect of inclusion of these results in analysis would likely have been a decrease in total effect size and would have added to the null-effect in the cohort studies as opposed to a positive effect in the case-control studies.

Exploration of heterogeneity: meta-regression

Meta-regression can observe associations of effect size with study level modifiers if there are enough studies included. We assessed the modifying effect of 3 pre-specified factors on our results in a random effects meta-regression analysis for the 5 year exposure outcome.

- Types of occupation: nurses versus other occupations
- Site of the study: high income countries (according to the IMF definition) versus LMIC.
- Shift system – rotating versus fixed shifts.

We further assessed the effect of study design to see if the results were similar to the subgroup analysis. None of the factors were found significantly related to risk for breast cancer (table 4).

Table 4: Random effects metaregression for the 5 year exposure outcome

Model covariates	Relative risk	P value	95% confidence interval
LMIC versus High income country	0.99	0.962	0.55 - 1.77
Nursing versus Industry	1.13	0.553	0.70 - 1.83
Nursing versus Various occupations	0.97	0.849	0.66 - 1.43

Fixed and rotating system versus Rotating shift system	0.96	0.793	0.64 - 1.43
Rotating shift system versus any shift system*	1.02	0.948	0.58 - 1.76
Cohort versus case-control design	0.96	0.829	0.62 - 1.48

*any=shift system was not reported

Sensitivity analyses

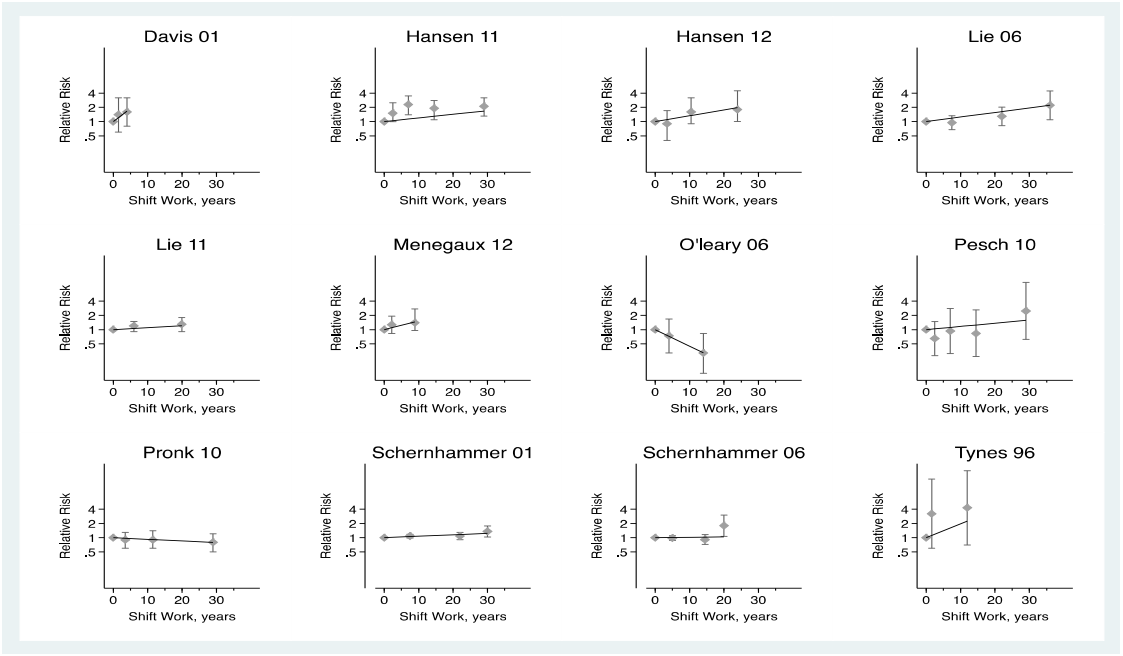
Fixed versus random effects

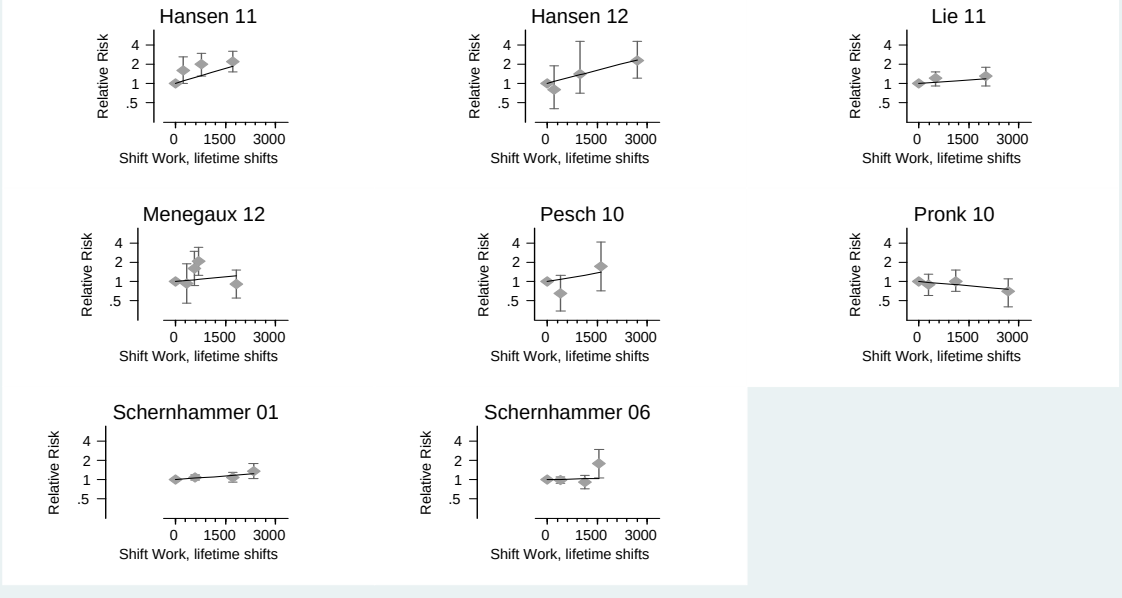
As specified in protocol we tested our model assumption in fixed effect analyses. The results of fixed effect analyses were similar to random effects analyses but with smaller confidence intervals (5 year exposure= RR 1.06, 95%CI 1.04 - 1.08; 300 shift = RR 1.03, 95%CI 1.01 - 1.05). Because the results were not different and there was significant heterogeneity we chose the random effects model.

Assumption of a linear model

To test our assumption of a linear relationship between night-shift work and breast cancer we analyzed individual study estimates with their exposure doses were plotted to see if any pattern was visible in terms of dose response in individual studies. Cohort studies with prospective exposure assessment found no relationship and the dose response varied among case-control studies. These individual graphs are presented in figure 4. Overall trend which is linear is presented in figure 5 and 6.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.

Figure 4: Dose response in individual studies- years of night-shift work and life-time shifts





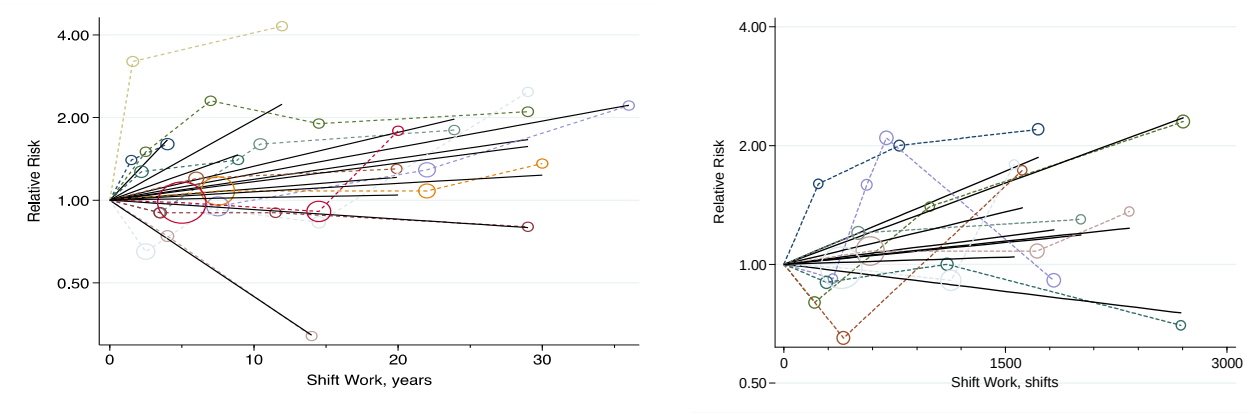


Figure 5: Linear dose response relationship in all studies included in meta-analysis with 95% confidence intervals

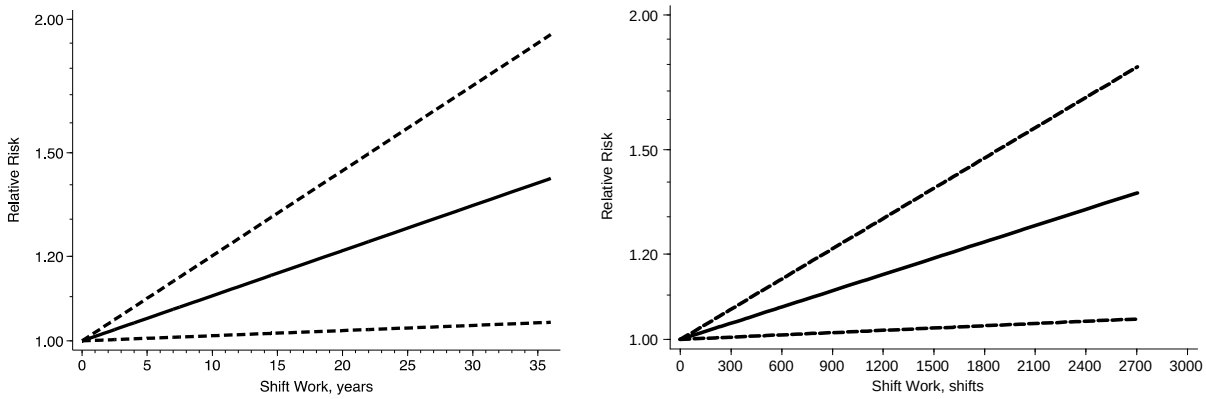


Figure 6: overall trend in studies include in meta-analysis

Excluding low quality studies

Restricting the result to the five moderate quality studies 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).

Modeling high exposure categories (post-hoc)

We expected that attributing the risk for that high open end category to a lower dose would make the slope steeper, yielding a higher incremental risk ratio for an individual study, however this did not influence

the results of the meta-analysis. Capping the highest exposure categories did not change the results significantly (random effects 5 yr RR = 1.06 (95%CI 1.0-1.1).

Two studies (Davis et al. 2001; Hansen et al. 2011), reported incremental risk per year. These reported values were used as a check of ourdose calculations. Our model provided similar values for both studies: 5 year RR 1.09 (95% CI 1.02- 1.17) compared to 5 year RR 1.05 (95%CI 1.02 – 1.07) reported in Hansen 2011 and 5 year RR of 1.88 (95%CI 0.82-4.3) compared to 5 year RR 1.84 (95% CI 1.05 – 3.22) reported in Davis 2001.

Median exposure in included case-control and cohort studies

Median exposure dose in nine case control studies was 4 years and the predicted relative risk at this exposure was 1.07 (95%CI, 1.02- 1.12). Similarly, median exposure in the three cohort studies was 9.5 years and the corresponding relative risk was 1.02 (95%CI, 0.97- 1.1). (figure 7). What is clearly visible in the figure is the difference in effect between the two study designs. At the same level of exposure the case control studies produce a much higher risk than do cohort studies.

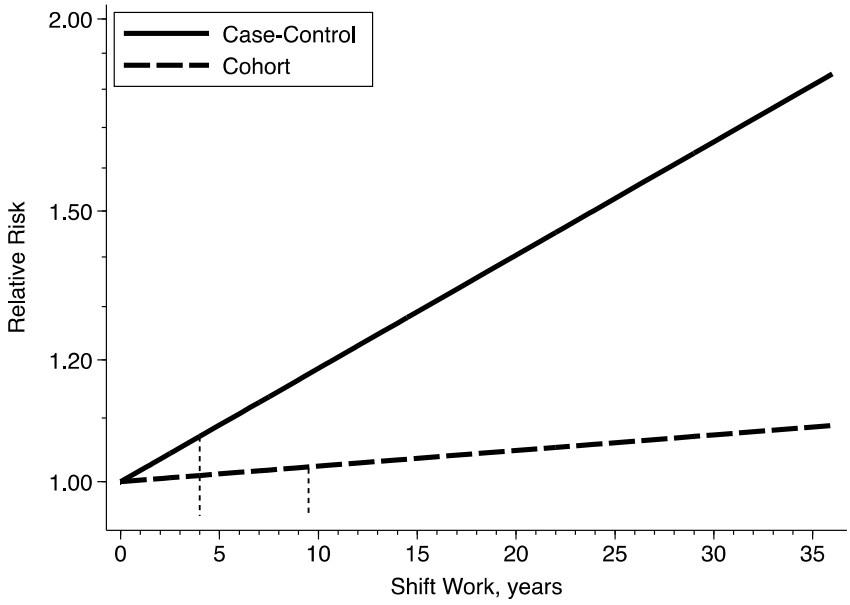


Figure 7 Effects estimates for median exposures across studies in case control and cohort studies

Publication Bias

Visual assessment

Visual assessment of publication bias shows that small studies are missing on the side of no effect. Fig 6.

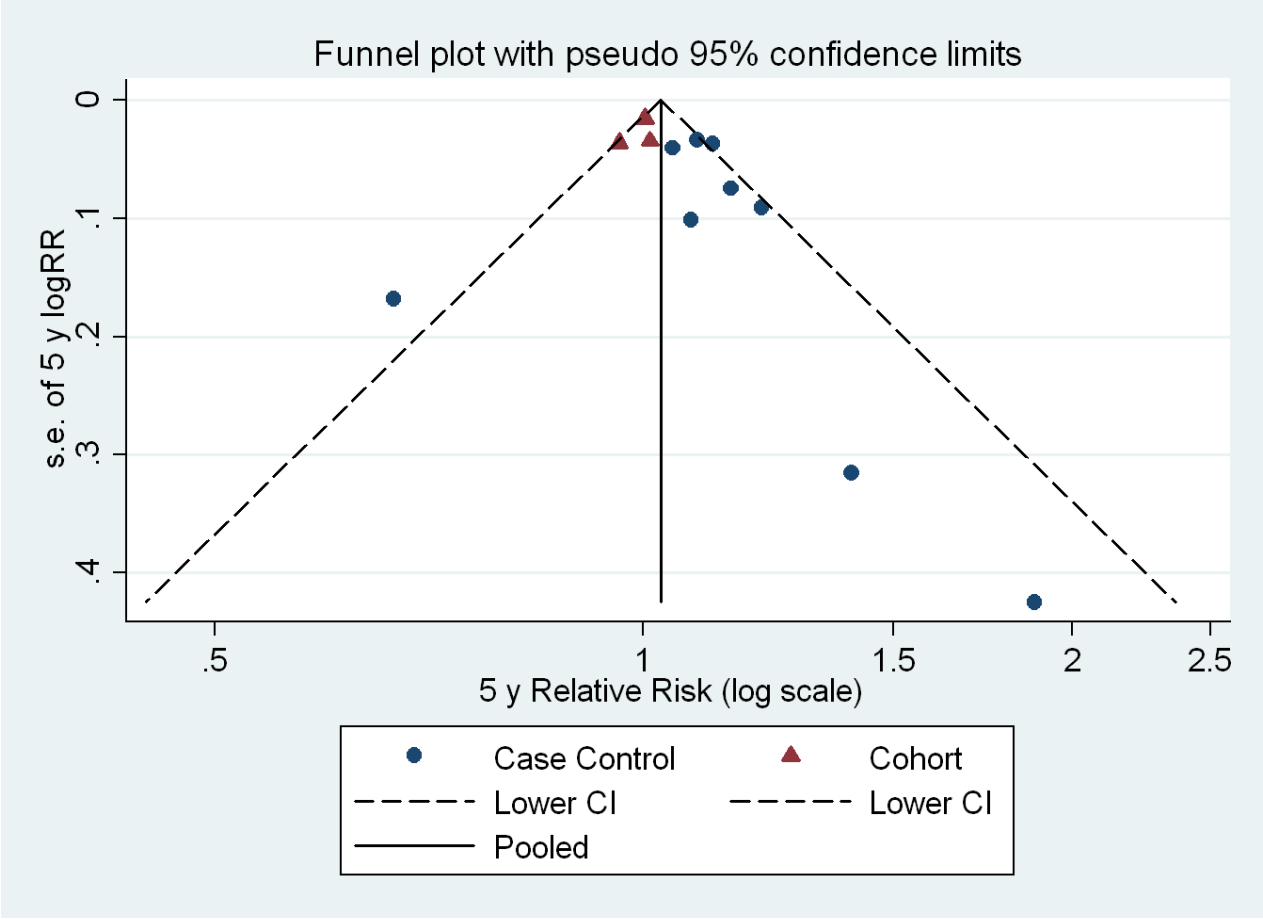


Figure 6: Funnel plot of 12 included studies

We tried to avoid publication bias by looking for unpublished studies in the grey literature and by contacting authors and experts. Information on these is reported under studies ongoing or awaiting classification. However we cannot be sure that all unpublished studies have been identified.

Statistical assessment

Results of the Egger test did not indicate small study effect (Egger's Coefficient=0.94 (95%CI -0.7 to 2.6, p=0.24).

Strength of the evidence

- According to the GRADE approach we judged the evidence of very low quality.

Outcome	Limitations	Advantages	Quality of evidence
Duration of exposure in years	Risk of bias/ design limits Very serious limitation	Large or very large effect No advantage	Very low
	Inconsistency Serious limitation		
	Indirectness No limitation	Dose Response No advantage	
	Imprecision Serious limitation	Confounding does not reduce effect No advantage	
	Publication bias Size of limitation unknown, likely large	Spurious if no effect observed Unlikely spurious- no advantage	
Life time number of night-shifts	Risk of bias/ design limits Very Serious limitation	Large or very large effect No advantage	Very low
	Inconsistency Serious limitation		
	Indirectness No limitation	Dose Response No advantage	
	Imprecision Serious limitation	Confounding does not reduce effect No advantage	
	Publication bias Serious limitation	Spurious if no effect observed Unlikely spurious- no advantage	

- Danish Occupational Medicine Association Approach

According to the approach of the Danish Occupational Medicine Association to grade the strength of causality, there is insufficient evidence of a causal association (grade 0). This means that the available studies are of insufficient quality and consistency to permit a conclusion of presence or absence of a causal association, largely due to poor exposure assessments in almost all studies and difference in results by

study design (see appendix E for details). Causal associations are best established in prospective cohort studies and the results from such studies in this review show no association.

4. Discussion

Summary of main results

Based on a meta-analysis of 12 of the 16 included studies, we found an effect of duration of exposure or of cumulative number of night-shifts with an incremental risk increase of 1.05 (95% CI, 1.01 - 1.10) with every five year of shift work exposure regardless of intensity. This means a risk of 1.4 (95%CI, 1.07-1.8) after 30 years of exposure. A risk of 1.04 (95% CI, 1.0 - 1.1) was seen per increase of 300 shifts. However, the relative risks were different between cohort and case-control studies with cohort showing no effect and case-control studies showing a larger effect. Sensitivity analysis including only studies at lower risk of bias did not change these results. Neither did spline or log transformation of data, or fixed effect sensitivity analysis. Case-control studies consistently produced bigger effect but with significant heterogeneity. Based on the Danish OMS approach the strength of the evidence is insufficient for causality and according to the GRADE approach, it is very low quality.

Overall completeness and applicability of the results

Our search was comprehensive, searching for all studies irrespective of publication or language status. We did not find a strong indication of publication bias in statistical tests. Nevertheless, we cannot be sure if all studies have been found. The funnel plot shows that small studies are missing especially those showing no effect. We found many studies carried out 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, in the world, there exist many more of such registers that are still untapped and therefore we believe that the included studies alone form an incomplete picture (Ioannidis 2012). This implies uncertainty about inclusion of all existing evidence.

Many studies referred to nurses and few to the general population- therefore it is likely that the results are more applicable to nurses. Although occupation had no significant modifying effect on our results in the meta-regression this can be attributed to few observations in the analysis. Similarly most studies were from high income, white populations and thus the results apply largely to these.

Of the four included studies that could not be included in the meta-analysis, there is only one with good exposure assessment and of moderate quality (Li 2011). The addition of this large nested case control study would have increased the precision of our results. The other three studies in our opinion have an arbitrary

allocation of shift work exposure and therefore we do not think these should contribute to the overall evidence on risk of breast cancer when comparing night work with day work.

Quality of the evidence

This is the first systematic synthesis of evidence on the question under study that included a full quality assessment following the accepted guidelines for this research method. The evidence was found to be of moderate to low quality.

The most important risk of bias in the studies included in the review was the exposure measurement. No study except Li 2011 used quantitative prospective measurement of shift work. Exposure measurement by interviews or questionnaires might not correctly assess the time worked in shift work and we do not know of any validation studies conducted regarding these. Although there are questionnaires for assessing impact of shift work on worker general health such as the Standard Shiftwork Index and Shift work Survey, these have also been found lacking in construct validity (Smith et al. 2001; Tucker et al. 2008).

Some improvements in validity were probably achieved with repeated questionnaires in the two cohort studies (Schernhammer 2006, Knutsson 2012). Similarly, use of self-report complemented by expert assessment/categorization can improve the validity of exposure assessment in case-control studies (Teschke et al. 2002) and this was employed in Pronk 2010. 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 to give valid measures of exposure for comparison with no exposure.

It is well 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, where the association of shift work and breast cancer has gained a lot of publicity, one could easily imagine that a woman with breast cancer better recalls and reports her shift work exposure than a woman without breast cancer. Given that in most work places and particularly in health care organizations the schedules and occurrence of shifts and hours of night work are planned and duly recorded, better data should be available in primary studies and validation studies should not be very difficult to carry out.

The cohort study design generally provides less biased results for causality especially when the exposure has been assessed before the disease has occurred. Of the six moderate quality studies we find exposure assessment of sufficient quality in only one (Li 2011) which is a nested case-control study. Pronk 2010

follows closely with an assessment less biased than the other studies. Although Knutsson 2012 had probably the most comprehensive prospective questionnaire this valuable information was not put to use in allocation of exposure. Therefore Li 2011 and Pronk 2010 are probably the more reliable in terms of their findings which are negative for both studies. However, both studies also included only Chinese participants. The lack of a relation between exposure and breast cancer in these studies could be due to both the better exposure measurement and the inclusion of Chinese women. Chinese women have a lower risk of breast cancer and could therefore, based on an unknown genetic disposition, be less at risk for the effects of shift work.

Limitations of our review

In studying causality of cancer due to an occupational exposure, a latency time is often of relevance and studies should take such a latency period into account by restricting the exposure to the limit of the latency periods for a disease (Greenland 2008). We could not take into account any latency period because the primary studies did not. If a latency period exists as has been shown for some other cancers, this could explain the lack of an effect. Li 2012, the only study that adjusted their results for lag of 10 and 20 years of exposure to rotating night-shifts, found no increase in the risk. Appropriate assessment of a potential latency period would require a much longer follow up than found in the included studies.

We used an established method of modeling category-specific risk estimates into an incremental risk estimate assuming a linear dose response. Unpublished information was sought to confirm our calculations and based on unpublished information we found that our model was accurate in all except the highest usually open category, where it overestimated the dose. We then sought average dose values for these open categories from authors and carried out a post hoc sensitivity analysis by using the lowest dose for these categories which did not change the results. We tested our model assumptions by applying cubic splines and log transformation of dose as and found the results to be similar to those when a linear response was assumed. Meta-regression analyses showed no significant influence of any of the potential effect modifiers such as shift system, location of the study and occupational variation. This may simply reflect the observational nature of these analyses which is dependent on the number of studies and type of data included.

Overadjustment for confounding in primary studies is a problem like underadjustment. However, we consider the effect of any potential confounding to be minimal on the relationship of shift work and breast cancer because usually for these established confounders of breast cancer, the association with night-shift work is weak. This was also evident when potential overadjustment by us in one study for one factor did not change the results of that study.

We could not include all studies we located and 5 of these are awaiting publication or ongoing. Addition of these to results in an update should improve the precision of our results.

Deviation from protocol

We had planned to present a meta-analysis in RevMan at protocol stage. However, during the process of the write up peer review suggested that it was not necessary (as results were the same) and hindered readability. Therefore we have not presented that analysis. We instead present forest plots produced in STATA only.

We could not perform the planned sensitivity analysis for publication bias by Shi and Copas for the entire sample of studies. For nine case-control studies this method showed no evidence of publication bias although visual inspection of the funnel plot shows a clear bias regarding publication of small studies with no effect of exposure. We therefore decided to use the other most used method (Egger's test).

It was anticipated that we will be able to perform additional adjustment of study results for confounders of interest. However, with the exception of one study suitable data were not available.

Agreements with other studies and reviews

Three previous systematic reviews have assessed the link between night-shift work and breast cancer (Megdal et al. 2005; Erren et al. 2008; Kolstad 2008). The findings of these older reviews are less relevant today due to the increase in numbers of studies. Furthermore we can see the following differences with the previous reviews that could explain a difference in the conclusions:

- In contrast to the previous reviews, the current review was done following an 'a-priori' protocol, although two reviews (Megdal et al. 2005; Kolstad 2008) reported some components of PICOS (participants, exposure in lieu of intervention, comparison, outcome and study design) for their review in the method section.
- Since more studies have become available since the last reviews in 2008, our review includes eight more breast cancer studies than Kolstad 2008, eight more than Erren 2008 and 10 more than Megdal 2008.
- None of the previous reviews modeled the dose-response relationship.
- Variation in defining population, exposure, comparison, and effect measures: we excluded studies if comparison was anything other than day work or another type/level of shift work, or if the exposure was not clearly night work.

- Searches were not comprehensive for any of the previous reviews and none of them sought unpublished studies. Publication bias was only assessed by Megdal 2005 which was also the only bias assessed in that review. A list of excluded studies was not provided in any of the three reviews and the table of characteristics of included studies was comprehensive only in Kolstad 2008.
- None of the reviews performed a formal risk of bias assessment for the individual included studies and therefore did not incorporate these assessments appropriately in the analysis and conclusions drawn. Erren 2008 and Megdal 2005 did not report any quality assessment, whereas Kolstad 2008 reported only a grading of the quality of their evidence for the causal relationship between breast cancer and night-shift work.
- All review processes were done in duplicate and consensus achieved.
- We used more rigorous exposure modeling to ensure better estimates of night work exposure and tested these models in pre-planned analyses.
- We differentiated between case-control studies and cohort studies. Only Erren 2008 made this subgroup distinction in their analysis.

Our findings are different from previous reviews in the respect that our overall result for risk per five year duration shows a small overall effect of night-shift work but consistently different between case-control and cohort studies. None of the included studies was at low risk of bias.

All previous reviews found the included studies to be homogenous which is contrary to our findings of significant heterogeneity. The Megdal 2005 review included six of the earliest studies and the fixed effect meta-analysis also included the large study of Hansen 2001 which is not included in our meta-analysis. Erren 2008 performed both fixed and random effects analyses and again found no heterogeneity based on Chi square values. However both reviews explored possible sources of heterogeneity in subgroup analyses, finding no significant differences. Kolstad 2008 did not include a meta-analysis. The author acknowledged that the number of studies was small and studies almost entirely were from nurse populations, that the results were likely biased but specific sources of bias could not be located.

Strength of association between shift work and breast cancer were found variable between the three reviews, and all different from our findings of a relatively small effect size (5% per 5 years), with large confidence intervals (95%CI 1 to 10%). Megdal 2005 concluded that shift work increased the risk of breast cancer by 50% (RR 1.51, 95% CI, 1.36–1.68). Erren 2008 also found a large effect in a random effects analysis of shift work vs no shift work (RR 1.7 95% CI 1.4 – 2.1). However they acknowledged that this could be a spurious finding due to exposure assessments being less than ideal. Our conclusion on less than valid exposure assessment is thus in line with them.

Kolstad 2008 used the same grading criteria as us (the Scientific Committee of the Danish Society of Occupational and Environmental Medicine). They found limited evidence of causal relationship between shift work and breast cancer whereas we found it to be insufficient. Again this may be because the number of studies has doubled since and studies with negative findings were published after 2008.

In addition to these three systematic reviews, the IARC monograph on shift work and cancer (IARC 2010) included eight primary studies on humans and one meta-analysis and concluded that night-shift work with circadian disruption is potentially carcinogenic due to consistent modest increase in risk seen in 6 of the eight studies. However, methods of searching and appraising studies were not reported and no narrative or quantitative systematic summarization of studies was done.

Implications for practice

Based on low quality of evidence, difference in effect by study design, and wide confidence intervals we cannot rule out a relationship between shift work and breast cancer. The uncertainty can only be resolved by more and better quality data. Evidence from the two Chinese studies indicates no increased risk for this population.

Implications for research

We need studies in which exposure should be measured in an objective way before the disease has occurred. Validation studies of interview and questionnaire data compared to objective prospectively collected shift work data are needed as well to find out if and to what extent recall bias occurs. Prospective cohort studies will add more to the evidence than case-control studies.

The definition of the term night-shift work can be made more global so as to allow comparisons that reflect best the nature of occupational exposure to night time working. One way to do this is to separate the term shift work from night work. Where shift work means work organized in shifts of any nature and night work means working after sun down at a certain minimum frequency/ intensity for a minimum period of time (years/ months). For example, exposure to night-shift work can be work between 8 pm and 6 am (thus excluding regular workday as much as possible) at least three times in a month (in rotating shifts) for minimum 6 month duration either rotating or fixed. This includes all three important elements of the IARC advice and may constitute a comprehensive definition of night-shift work.

Future studies should better define and preferably compare rotating and fixed night work to see if a difference in risk exists. Furthermore, there may be a threshold of 15 or 20 years of night work for increasing the cancer risk and this should be studied. More studies should factor in tolerance to shift work

(diurnal preference) when studying risks of cancer as done in Hansen 2012. Tolerance is variable within shift workers and may be a confounder as well as an effect modifier.

5. Appendices

Appendix A

Breast Cancer and Shift Work - Search Strategy PubMed April 2012

8) #1 AND #77) #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]

Appendix B-1

Inclusion exclusion criteria template _ exposure to night-shift work or recurring night-shifts as a causative factor for breast cancer

Comparison: shift work vs day work

REVIEWER ID:

Study ID first author with yr of publication (for the most informative report if not clear)	Study Design and allocation Inclusion: cohort study (people followed up in time until outcome appears) OR case-control study (history elicited regarding exposure to shift work from patients breast cancer) Exclusion: Cross-sectional surveys studies with no	Participants Inclusion: Female workers Exclusion: flight attendants, pilots or other airline crew, women workers exposed to known occupational carcinogenic factors in addition to shift work (e.g. chemicals at work) Irrelevant: Men	Exposure: Shift Work, which included hours before 6.00 am or later than 8.00 pm. whether rotating or fixed shifts. Inclusion: any duration/intensity measured on any scale We will include studies/ exposure as reported by authors to be 'shift work' so as to include the entire range of evidence available. Exclusion: known carcinogenic exposures in addition to shift work (e.g. radiation, chemicals at work place)	Control group: Inclusion: day work between 6 am to 8 pm or an alternative shift work schedule Exclusion: majority general population, un employed, house wives	Outcomes Inclusion: Incident Breast cancer diagnosed by biopsy clearly stated or safely assumed from report (hospital records, insurance records) Exclusion: self report/not reported/ likely from report that diagnosis of breast cancer was not based on biopsy, secondary outcomes reported only (melatonin, estrogens levels)	Notes e.g. other potential reasons for exclusion	Included / excluded/ unclear

	control group				Irrelevant: Outcomes other than incidence of Breast cancer (mortality, severity, intermediary outcomes)		

Appendix B-2

DATA Extraction Form Shift Work and Breast Cancer Review

Notes for data extraction:

Please state **NR** in the response column if an item is not reported in the study

Adjusted values are preferred when provided compared to crude ones. if unable to judge please state next to the values or item, for example, 'not clear if adjusted'

Since data would be available in many formats a general rule is: when in doubt, take out as much data or information as possible. If a column does not seem to fit the data provided in the paper please describe in the authors words or your own with actual values. It is best to extract these variable data formats in the 'other' exposure assessment boxes provided.

In the risk of bias assessment the judgement boxes☐ are supplemented with description of situations where that judgement would apply. Also, text boxes are available next to high and low risk judgements for quotes from the study or your comments that made the decision possible. Any explanations would enable quick agreements possible and are encouraged.

Please cite the references(author 1, title, journal, year, volume and pages) to other potentially relevant studies cited in this included study here :

Any additional report(s) of the same study used /to be used for data extraction (Author 1, title, journal, year, volume, pages) should be indicated here:

Any info not available in the paper that is needed from authors should be cited here:

PLEASE SEND THE COMPLETED FORM BACK TO sharea.ijaz@ttl.fi

DATA Extraction Form Shift Work and Breast Cancer Review- prospective/ cohort study

Study Characteristics

Your name sharea Study ID (author year) Date:

Aim of the study		
Study design (mark at least one that best describes and any other that may apply)	☐Cohort (prospective) study with concurrent controls ☐Cohort (retrospective) study with concurrent controls ☐Case-controlled (retrospective) study ☐Cohort (prospective) study with historical controls Mark if the study had defined populations that were prospectively followed in an attempt to determine distinguishing population characteristics with historical controls ☐Nested case-control Mark if the study started with the identification of persons with a disease of interest and a control (comparison, referent) group without the disease that were identified within the cohort of the subjects, participants in prospective cohort study. The relationship of an attribute to the disease was examined by comparing diseased and non-diseased persons with regard to the frequency or levels of the attribute in each group. ☐Other-specify Specify reported study design with terminology different from the definitions of the National Library of Medicine (described above)	
Study Country		
Participants		
	Exposed	Unexposed
Sources of participants		
Number of Participants (enrolled)		
Number of Participants (analysed)		
Age range or Mean +SD in yrs (describe if reported in another way)		
Gender		
Occupation		
Industry		
Attrition rate		
Excluded from analysis		

Shift Work Exposure Information	
Source of information on shift work exposure (Interviews etc)	Exposed Unexposed
Shift Work Description (eg night-shift work)	
Shift Work Definition (eg between 0.00 and 6.00 hrs)	
Unexposed/Reference Category definition (non-shift work)	
Shift Work Exposure Other categories reported	category name and / or description
Shift system type (mark all that apply)	Rotating☐ Forward rotating☐ Backwards rotating☐ Fixed (describe) Other☐ (describe) Not reported☐
Average Shift exposure duration (yrs m ± sd)	Exposed Unexposed
Average Shift exposure intensity (non-day shifts/month)	Exposed Unexposed
Average Cumulative shift exposure (intensity x duration)	Exposed Unexposed
Other measure of shift exposure reported	exposure measure name cases controls
Confounders	

Confounding factors controlled for	Age ☐ BMI ☐ Ethnicity ☐ Parity ☐ Soc Ec Stat ☐ ☐Other			
Outcome DATA - histologically confirmed Incident Breast cancer				
risk per year of exposure increase	Crude RR 95%CI	Adjusted RR 95%CI		
categories of exposure duration	category name	RR	95% CI	
	cat			
	cat			
	cat			
	cat			
risk per unit of intensity increase (eg shift /mo)	Crude RR 95%CI	Adjusted RR 95%CI		
categories of shift work intensity (adjusted for confounders yes no)	category name	RR	95% CI	
	cat			
	cat			
	cat			
	cat			
	cat			
risk per year of cumulative dose increase (int * year)	Crude OR 95%CI	Adjusted OR 95%CI		
categories of cumulative dose (adjusted for confounders yes no)	category name	RR	95% CI	
	cat			
	cat			
	cat			
	cat			
	cat			

risk per year of other interesting exposure measure unit increase	Crude RR 95%CI	Adjusted RR 95%CI		
categories of other exposure name (adjusted for confounders yes no)	category name	RR	95% CI	
	cat			
	cat			
	cat			
	cat			
	cat			

Risk of Bias assessment

Text spaces are available next to the justification of high and low risk categories for your comment or a quote from the study that helped making the decision

Funding and conflict of interest

Risk due to Funding source of study	☐ high Industry (one or more corporate sponsors), Combined industry + Grant
	☐ low Grant/ not-for-profit sponsors
	☐ unclear Not reported
Risk due to role of funding organization in data analysis and interpretations of the results	☐ high Sponsoring organization participated in data analyses
	☐ low study was clearly not affected by sponsors
	☐ unclear Not reported

Risk due to conflict of interest	☐ high conflict of interest exists (at least one author)
	☐ low Reported not having conflict of interest or clear from report/ communication that study not affected by author(s) affiliation
	☐ unclear Disclosure not reported

Internal Validity

Definition of the exposure *(ideally according to IARC shift work should be measured in 3 aspects, duration of shift work (in years), shift work intensity (number of non day shifts per month), shift system (fixed or non fixed, forward or backward rotating).*	☐ high risk Definition of exposure/ case is categorical with an arbitrary threshold (e.g.1 yr or more, ever done night work) OR Definition covers only one aspect of exposure (start or end time of shift, duration, intensity, shift system)
	☐ low risk Definition included at least two of the aspects recommended by IARC ((1) shift system: rotating or fixed, forward or backward rotation (2) shift duration: number of years (Houssami et al.) (3)shift Intensity
	☐ unclear risk shift work is not defined in report (shift work or night work is used as a term without elaboration on what it stands for in the study)

Intensity/dose of exposure	☐ high risk Intensity/dose not assessed in the study
	☐ low risk Intensity/dose of exposure included in the definition/assessment of exposure.
	☐ unclear risk Intensity/dose assessment is not reported

Source to measure exposure	☐ high risk patient recall, medical or administrative records of job titles etc

	☐ low risk employers' prospectively collected database OR employees prospectively recorded data (logging charts/ diaries)
	☐ unclear Not reported

Measurement methods used for exposure assessment	☐ high risk subjectively measured: Reported by participants (interviews/questionnaires) subjectively measured: Proxy used to allocate exposure status (job matrix, job title)
	☐ low risk objectively measured: direct measurement of exposure (logging data, shift schedule data from the HR or employers records. prospective self measurement of exposure e.g. with diaries)
	☐ unclear risk not reported

Masking of investigators	☐ high risk Not obtained
	☐ low risk assessors were blind to exposure status in cohort studies and to case status in case-control studies
	☐ unclear risk Not reported

Reliability of exposure estimates- For prospective studies	☐high risk Intra-observer variability is reported by means of a subjective judgment of reliability
	☐low risk Good inter observer reliability achieved with reliability values reported/ not applicable for the measure used
	☐unclear risk Not reported
	☐ high risk The authors used different methods to measure exposure (shift work) in cases and controls
	☐ low risk The authors used same methods for cases and controls to measure exposure

	☐ unclear The authors did not state that the same methods were used to measure exposure risk factors, independent variable) in cases and controls

Confounding factors Factors that can modify the association between shift work and breast cancer	☐ high risk Major confounding factors/effect modifiers (Age, BMI, Ethnicity, Parity (number of children, age at first birth), and Socioeconomic status) were not assessed or assessed partially.
	☐ low risk Major confounding factors/effect modifiers (Age, BMI, Ethnicity, Parity (number of children, age at first birth), and Socioeconomic status) were assessed in full.
	☐ unclear risk Not reported

Measuring of confounding factors	☐ high risk Unknown validity to measure confounding factors OR Non-valid methods to measure confounding factors
	☐ low risk Confounders measured with valid methods
	☐ unclear risk Not reported

Attrition bias Loss of follow-up -cohort studies	☐ high risk Total loss to followup is larger than acceptable (20% or more) OR drop out differs between the groups by more than 10% OR the reasons for drop out are different for exposed and non exposed groups
	☐ low risk loss to follow up below 20% in total and not different between the two groups (up to

	10% difference)
	☐ unclear risk Not reported
Non response- For case-control studies	☐ high risk% of nonresponse differed among cases and controls OR % of non response reported for cases only OR reasons for non response not reported/ different between cases and controls
	☐ low risk % non response was reported for both cases and controls and did not differ in size and reasons
	☐ unclear risk Not reported

Analysis of the study Methods to reduce research specific bias	☐ high risk Authors did not obtain methods to reduce bias OR did not justify their choice of statistical models to reduce research specific bias
	☐ low risk Authors reported use of one or more methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring)
	☐ unclear Methods to reduce research specific bias not reported
Dose response analysis	☐ high risk Not assessed
	☐ low risk Dose response assessed in analysis
	☐ unclear risk Not reported

Reporting of the tested hypothesis	☐high risk Incomplete/ selective reporting of the tested hypotheses (compared to aim and objectives) AND/OR Crude estimates presented only
	☐low risk Adjusted estimates presented for all hypothesis tested as per aims
	☐unclear risk Unclear reporting of tested hypothesis

Sample size justification	☐high risk Not reported
	☐low risk Justification by authors

Following were the major domains where risk of bias was assessed: Exposure definition, Exposure assessments, Blinding of assessors, Reliability of assessments, Confounding, Attrition, Selective reporting, Analysis methods in the study (Research Specific Bias), Funding and Conflict of interest.

- Exposure definition was considered to be at low risk of bias if the definition included at least two of the four aspects recommended by IARC ((1) shift system: rotating or fixed, forward or backward rotation (2) shift duration: number of years shift Intensity (4) cumulative exposure over the subject's working life: duration X intensity (Stevens et al. 2010). The following exposure definitions were considered a high risk of bias: using a categorical definition with an arbitrary threshold (e.g.1 yr or more, ever done night work) OR a definition which covers only one aspect of exposure (start or end time of shift, duration, intensity, shift system)
- Assessment of exposure was considered at low risk of bias in a study if objectively measured: direct measurement of exposure (logging data, shift schedule data from the HR or employers records, prospective self measurement of exposure e.g. with diaries). 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). (Teschke K. et al 2002).

- For the blinding domain a study was given a low risk judgement 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 judgement 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 is judged to be at Low risk for cohort studies when good inter/intra observer reliability was achieved with reliability values reported or when measures used were objective such as log data. Study was considered at 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 judgement of Unclear.
- Confounder assessment was considered at two levels: whether at least 4 of the 5 major confounding factors/effect modifiers (Age, BMI, Ethnicity, Parity (number of children, age at first birth), and Socioeconomic status) were assessed completely (Low risk) or assessed partially (High risk), 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 at 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.
- In the domain of Attrition a total loss of participants (non-response in case-control studies) of 20% or more OR a dropout/non-response difference between the compared groups of 10% or more OR the reasons for dropout/non-response not given/different led to a judgement of high risk. Conversely a below 20% loss in total and up to 10% difference in dropout/ non response between the two groups was considered low risk. A lack of information led to a judgement of Unclear.
- Selective reporting of results 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 marking 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 pertains to analysis of the study and includes three aspects: Methods used in analysis to reduce bias due to research design (these methods include standardization, matching, adjustment in multivariate model, stratification, and propensity scoring), analysis included assessment of dose response in someway (subgroup, regression), and the sample size is justified by authors. When all three of these are at low risk of bias or two reviewers

agreed that unclear or high risk in one of these aspects in a particular study does not affect the results significantly, the whole domain is given a low risk judgement. Authors were contacted to clarify any ambiguity.

- Funding 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 at low risk of bias. If one of these factors was high risk the study was marked high risk and if one of these was not reported the study was marked at unclear risk.
- For conflicts of interest, a study was considered at low risk if there were no conflicts of interests to be declared, or if declared interests were not deemed conflicting (as assessed by two reviewers), at high risk if one or more authors had indicated a conflicting interest, and unclear when the information was not provided.

For the overall assessment of the risk of bias per study we had the following considerations.

It is clear that in terms of exposure the shift work schedules have the most relevant impact on the biological rhythm, circadian desynchronization and re-adjustment, as well as sleep deprivation and recovery, thus on health. This has led the IARC working group (Stevens et al. 2010) to propose the collection of more detailed information about these parameters for the risk characterization, in particular the amount and number of consecutive night-shifts, direction and speed of rotation, start and end time of shifts, and so on.agreed Thus, exposure definitions and assessments are obviously the most important domains for risk of bias in our review. Similarly the amount and type of confounders taken into consideration may affect significantly the reliability of a study in the context of the current review. Therefore, we considered domains into two hierarchical groups:

- 1st group: Exposure definition, Exposure assessments, Reliability of assessments, Confounding, Analysis methods in the study (Research Specific Bias)
- 2nd group: Blinding of assessors, Attrition, Selective reporting, Funding and Conflict of interest

Then we rated the risk of bias in a study as a whole as follows:

- low risk of bias: low risk in all 5 domains of the 1st group and at least 2 of the domains from the second group.

- moderate risk of bias: low risk of bias in at least 4 domains in 1st group and 2 domains in second group.
- high risk: less than 4 domains from first group at low risk of bias

Appendix C

Confounding in the link between Shift Work and Breast Cancer

In epidemiological research on the relation between shift work and breast cancer confounding factors are a potential threat to the validity of the studies. Confounding factors are usually defined as factors that are related to both the exposure of interest, i.e. shift work, and the outcome of interest, breast cancer. In a systematic review of studies of shift work and breast cancer it is important to check, estimate and adjust for confounders. Therefore, we started with a literature search for confounders of the relation between shift work and breast cancer. Risk factors for breast cancer are fairly well known and incorporated into for example breast cancer risk assessment tools (www.cancer.gov/bcrisktool). For shift work, this is less clear. This is partly due to the lack of clarity on how to measure shift work exposure and what is the potential causal mechanism that would lead from exposure to health outcome. Factors associated with the cumulative duration of shift work could be different from those associated with exposure to light at night. Instead of being a confounder, factors related to shift work could also be intermediary factors that just mediate the causal effect. Being in shift work is associated with a higher BMI than being in day time work only. High BMI could both be regarded as a confounder and as an intermediary factor.

We want to assess and adjust for potential confounders that were found to be associated with shift work (a significant difference in distribution of the factor between shift workers and day workers) and were a major risk factor (30% or more) for breast cancer.

Types of confounders

Association of exposure to shift work with breast cancer can be easily confounded by other risk factors for breast cancer such as age, lack of exercise, obesity, alcohol intake or other dietary factors that are both associated with shift work and breast cancer.

In essence these are factors which, if associated with both the exposure (shift work) and the outcome (breast cancer), may partly explain the effect on breast cancer attributed to shift work. However if the results after adjusting for these factors still indicate an association between shift work and breast cancer then shift work may well be a causative risk for breast cancer.

Age, sex, ethnicity and social (or socioeconomic) status are the most common confounders for any health or disease state, and virtually any exposure. Of these four universal confounders, even though not exclusively, breast cancer does occur predominantly in female sex. Therefore this review will only consider studies addressing the female population.

Other possible characteristics of shift workers which are also independent risk factors for breast cancer can be considered in two categories: reproductive factors and non reproductive life style factors. We will now discuss these in detail.

Age, Ethnicity, and SES

Age is considered the most important risk factor for breast cancer: the risk increases with increasing age with 81% of cases occurring in women over 50 years of age, with nearly half of the cancers occurring in the age bracket of 50 to 69 years (Cancer Research UK 2011).

The relation between age and shift work is less clear. Data from a survey of European workforce characteristics suggest that there is a gradual reduction in proportion in shift work from 25 years to 55 years, with nearly 20% in shift work between ages 25 and 39, 16% between age 40 and 54, and 10% above age 55 (European Foundation for the Improvement of Living and Working Conditions. 2003). A similar effect is seen from US data on shift working population (IARC 2010). This may be a healthy worker effect, where sick members of the work force may have left shift work (or work per se) as they age. Below the age of 25, the shift workers make up the highest proportion of men who think their job does not affect their health however this proportion drops sharply after age 35 (European Foundation for the Improvement of Living and Working Conditions. 2003). A large population based cohort study also indicated that proportion of shift working women was higher at age 30 (42%), but decreased to 32% and 27% at ages 40 and 50 respectively (Karlsson et al. 2001). This means it is important to address this effect of age in studies by adjusting for age and also for cumulative exposure to shift work in order to get precise estimates of cancer risk for various age and exposure levels.

Breast cancer incidence is variable by *ethnicity*. It is lower for Asian females than Whites in the UK (Cancer Research UK 2011). Age adjusted US data shows that White women had the highest incidence rate (121/100,000) for breast cancer followed by Black (117/100,000), and the least for Asian women (83/100,000) (http://www.cdc.gov). Shift work is significantly more prevalent in African Americans than any other ethnicity and least prevalent in whites in the USA (IARC 2010). Thus it seems logical to adjust for the Black ethnicity when assessing the effect of shift work on breast cancer.

For *socioeconomic status*, studies from US indicate that socioeconomic status is indicative of breast cancer risk with higher social status increasing the risk for breast cancer even when adjusted for ethnicity (Yost et al. 2001, Krieger et al.1999, Vainshtein 2012, Pudrovska and Anikputa 2011). Breast cancers rates are also higher in high income countries (Jemal et al. 2010). This can be explained by factors such as late first pregnancy, higher use of hormones (HRT/OC) and lower parity, along with better access to screening and treatment in affluent countries (Jemal et al. 2011). Socioeconomic characteristics among shift workers are not as clear. However the Nurses Health study data suggests that being in rotating shift work longer than 15 years is associated with low education of the worker (5% educated beyond bachelors' degree compared to 9% in controls), and that of her husband (29% studied beyond high school compared to 41% in controls) (Schernhammer et al. 2001). It is possible that shift work, because of better monetary compensation attracts women from a lower or at least somewhat different social status compared to day work. Still, being in a 24 hour society that we are today, it is possible that such a difference does not exist now even if it did some years ago. This may be particularly true for certain occupations such as healthcare and hospitality (hotels etc.) where rotating in various shifts for at least some duration of one's work life is inevitable.

Reproductive factors

Age at menarche, age at first birth, age at menopause, parity, use of HRT/OC, high estrogens and prolactin levels, previous breast disease and family history of breast cancer have all been found to be risk factors for breast cancers in systematic reviews and meta analyses of observational studies.

Factors unlikely to be confounders

Of all the reproductive factors, prevalence of early menarche and mean age at menopause were found to be the same in shift workers and non shift workers (Schernhammer et al. 2001), even though these factors are strongly associated with breast cancer (Garcia-Closas et al. 2006). These genetically determined factors are believed to be unlikely related to shift work and thus unlikely confounders in causal relationship of shift work with breast cancer. Similarly, previous breast disease and family history of breast cancer are both associated with increased risk of developing breast cancer (Hartmann et al. 2005, Page et al 2003, Pharoah, et al. 1997,(Collaborative Group on Hormonal Factors in Breast Cancer 2001). However, it is not known if a

relationship with shift work exists with benign breast disease or with family history, and a link seems unlikely due to genetic determination of these factors.

Use of oral contraceptives increases the risk in premenopausal women by 20% according to a recent meta analysis (Kahlenborn et al. 2006). The risk increase is about 66% with current use of HRT when compared to past or never use (Beral 2003). However, the use of OC/ HRT was found equal in shift workers and controls in a large cohort study (Schernhammer et al. 2001).

High *estrogens* levels in blood have been associated with breast cancer in prospective studies and in a meta analysis (The Endogenous Hormones Breast Cancer Collaborative Group 2002; Rod et al. 2009). Significantly higher serum estrogens levels have also been found in a cohort of post menopausal Japanese shift workers (Nagata et al. 2008), indicating that this may be a factor associated with both shift work and breast cancer. A similar relationship has been seen for prolactin levels, that is, higher levels are seen in both shift workers (Weibel et al. 1998) and in patients developing breast cancer (Eliassen et al. 2007). However, these biomarkers are considered intermediate outcomes in the causal pathway of breast cancer and are unlikely to be measured in studies assessing shift work.

Of the remaining reproductive risk factors, parity, age at first birth, Horomne replacement therapy (HRT), and number of children has been seen associated with shift work consistently:

Parity

Breast cancer risk is 30% higher in women who have never given birth (Ewertz et al. 1990). Shift work has been linked with higher likelihood of sub fecundity and subfertility compared to non shift worker females by some (Bisanti et al. 1996; Schernhammer et al. 2001; Zhu et al. 2003) but not by others (Feskanich 2009). Data from the NHS study indicated that 7.3% of women in rotating shift work for 1-14 years were nulliparous compared to 5.7% in controls (Schernhammer et al. 2001). A similar difference was found in a more recent report as well (Viswanathan et al. 2007).

Age at first birth

Women who had their first child after the age of 35 years had a 40% higher risk than those who did so before 20 years of age (Ewertz et al. 1990. the relative risk increases by 3% for each year of delay (Collaborative Group on Hormonal Factors in Breast Cancer 2002). Women in shift work may be those who wish to delay having children. Or, the nature of work in shifts, which is considered to disrupt family activities (Skipper et al. 1990), may predispose them to delay in having children. Furthermore, it has been reported that more educated working women delay having children for career (Heck et al. 1997) and that child bearing rate is lower in shift workers (Lin et al. 2001). Between 7.4 to 9% of rotating shift workers were over 30 years of age at first birth compared to 6.9% in controls in the NHS study cohort (Schernhammer et al. 2001).

Non reproductive life style factors

The known risk factors for breast cancer include a greater body weight, a high BMI, low physical activity, high fat intake, smoking, and alcohol intake.

BMI

Over weight (BMI>25) and obese(BMI>30) post menopausal women have up to 30% more chance for breast cancer than those with BMI less than 25, however the same factor is protective in premenopausal

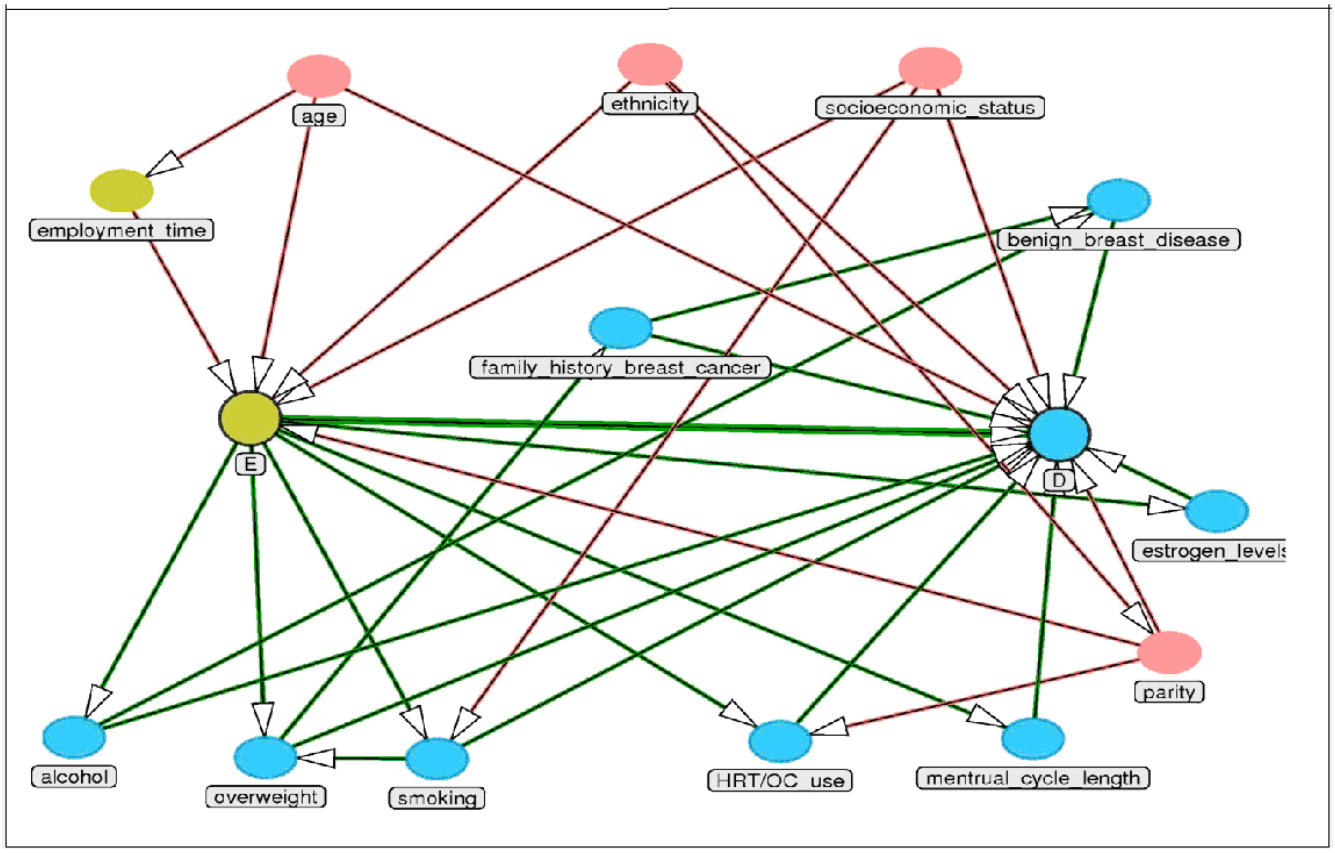
women with a 20% risk reduction. BMI greater than 30 was significantly more prevalent among shift working women compared to non shift working women at all index ages (30, 40, 50, and 60) in a large cohort study (Karlsson et al. 2001). *High fat intake* is related to higher breast cancer risk in post menopausal women but protective in premenopausal women (Boyd et al.) 2003, Rod et al. 2009, Turner 2011), much like obesity. Similarly, higher p*hysical activity* is related to lower risk of breast cancer (Monninkhof et al. 2007). Prospective and cross sectional studies indicate that shift workers are more likely than non shift workers to be overweight and obese, and have lower physical activity levels compared to non shift workers (Kivimaki et al. 2001), (Zhao et al. 2011),(van Drongelen et al. 2011), (De Bacquer et al. 2009), (Schernhammer et al. 2001). However, (Feskanich et al. 2009) found a higher level of physical activity among rotating nightshift workers than those who did not do rotating night-shift work. A systematic review (Zhao 2008) found poor health habits such as unhealthy food intake and smoking in shift workers however, only one included study addressed fat intake in this review and did not find an association of shift work with fat intake. Since change in fat intake along with levels of physical activity can be directly related to changes in body weight, it is probably better to consider the BMI/ body weight as a factor rather than its likely precursor i.e. fat intake, simply because it will be easier to measure validly and compare as well as more likely to be reported in observational occupational health studies.

Smoking and Alcohol

An established risk for breast cancer is *alcohol intake* raising the risk by 10% for each additional daily 10g consumption of ethanol (Key et al. 2006). Shift work was not found associated with increase in alcohol intake in recent studies (Kivimaki et al. 2001; Hermansson et al. 2003). Schernhammer et al. (2001) report that rotating shift work longer than 15 years is associated with a decreased daily consumption of alcohol (5.5$\pm$ 11g per day), whereas the daily consumption is equal among non shift workers (6.3$\pm$ 11 g per day) and those who have been in rotation shifts for less than 15 years (6.5$\pm$ 11 g per day). Compared to alcohol, a smaller (9-16%) increased risk with past or current *smoking* (compared to never smoking) is seen relative to breast cancer (Khuder et al. 2001; Cox et al. 2011; Luo et al. 2011). Shift workers are more likely to take up smoking than non shift workers (van Amelsvoort et al. 2006) and this difference in smoking likelihood is more pronounced for older shift workers than those at the beginning of their careers indicating that this may be a result of the shift work exposure and not the reason for selecting shift work (Kivimaki et al. 2001).

Conclusions:

We wanted to define adjustment sets that exclude indirect effects (mediated via lifestyle changes) of shift work on breast cancer. A directed acyclic graph (DAG), to reduce the degree of bias for the effect estimate (Shrier et al. 2008) created with DAGitty (Textor 2011) (http://www.dagitty.net/) (see Fig 1) including all potential confounders for breast cancer and shift work led to the following conclusions:



Legend: exposure, outcome , ancestor of exposure, ancestor of outcome, ancestor of exposure *and* outcome, causal path , biasing path

Fig 1: Directed acyclic graph for relationship between shift work (E) and breast cancer (D).

1. The appropriate adjustment set for estimating the total effect of shift work on breast cancer would include: age, ethnicity, parity, socioeconomic status. Adjusting just for these "true" confounders (factors that can causally influence shift work as well as breast cancer- marked in pink in the DAG) would be preferable if we were interested in the effects of preventive measures. If, for example, in a hypothetical company night-shift work was abolished, this could in fact also have effects on smoking, alcohol consumption etc.

2. However, if we are interested in "patho-physiological" effects of shift work (effects potentially/allegedly produced by shift work that are known breast cancer risk factors), we want to adjust for another comprehensive set of factors: HRT/OC use, alcohol, oestrogen levels, menstrual cycle length, overweight, parity, and smoking, in addition to the 'true' confounders. Of these set of 'pathophisiological effects' of shift work it is useful to adjust for those which show a significant and/or consistent relationship with shift work: factors for which a difference in distribution between day work and shift work populations exists according to previous research.

Based on distribution of all breast cancer risk factors in shift work population compared to day workers, we found that only high BMI (overweight and obese), and low parity (nulliparity and delayed parity) were significantly associated with shift work populations.

Thus the list of factors most significantly related to both breast cancer and to shift work, and therefore confounders that we consider important are:

Age,

Ethnicity,

Socioeconomic status,

Parity (number of children, age at first child),

BMI (overweight, obese)

The results from the included studies will be adjusted for these factors for our analysis.

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Appendix D

- **Degree of evidence of a causal association between an exposure to a specific risk factor and a specific outcome (Danish Occupational Medicine Association Approach)**

The following categories are used.

+++ strong evidence of a causal association
++ moderate evidence of a causal association
+ limited evidence of a causal association
0 insufficient evidence of a causal association
- evidence suggesting lack of a causal association

Description of categories:

Strong evidence of a causal association (+++):
A causal relationship is very likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It can be ruled out with reasonable confidence that this relationship is explained by chance, bias or confounding.

Moderate evidence of a causal association (++):
A causal relationship is likely. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It cannot be ruled out with reasonable confidence that this relationship can be explained by chance, bias or confounding, although this is not a very likely explanation.

Limited evidence of a causal association(+):
A causal relationship is possible. A positive relationship between exposure to the risk factor and the outcome has been observed in several epidemiological studies. It is not unlikely that this relationship can be explained by chance, bias or confounding.

Insufficient evidence of a causal association (0):
The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of a causal association (-):
Several studies of sufficient quality, consistency and statistical power indicate that the specific risk factor is not causally related to the specific outcome.

Comments:
The classification does not include a category for which a causal relation is considered as established beyond any doubt.

The key criterion is the epidemiological evidence.

The likelihood that chance, bias and confounding may explain observed associations are criteria that encompass criteria such as consistency, number of 'high quality' studies, types of design etc. Biological plausibility and contributory information may add to the evidence of a causal association.

Appendix E

Appendix GRADE Approach to Assessing the Evidence

GRADE Working Group: Grades of Evidence

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

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

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

Very low quality: We are very uncertain about the estimate.

GRADE Working Group: Rating the Quality of Evidence

Limitations to Evidence

Explanation of Parameters

Parameter 1: Limitations to design of randomized controlled trials

Limitation	Explanation
Lack of allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (major problem in "pseudo" or "quasi" randomized trials with allocation by day of week, birth date, chart number etc.)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Loss to follow-up and failure to adhere to the intention to treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other limitations	For example: stopping early for benefit observed in randomized trials, in particular in the absence of adequate stopping rules use of unvalidated patient-reported outcomes carry-over effects in cross-over trials recruitment bias in cluster-randomized trials

Parameter 2: Inconsistency of results or unexplained heterogeneity

When heterogeneity exists, but investigators fail to identify a plausible explanation, the quality of evidence should be downgraded by one or two levels, depending on the magnitude of the inconsistency in the results.

Inconsistency may arise from differences in:

populations (e.g. drugs may have larger relative effects in sicker populations)

interventions (e.g. larger effects with higher drug doses)

outcomes (e.g. diminishing treatment effect with time).

Parameter 3: Indirectness of evidence *(note: Indirect comparisons were not made in the present work)*

Indirect comparison – occurs when a comparisons of intervention A versus B is not available, but A was compared with C and B was compared with C. Such studies allow indirect comparisons of the magnitude of effect of A versus B. Such evidence is of lower quality than head-to-head comparisons of A and B would provide.

Indirect population, intervention, comparator, or outcome – the question being addressed by the guideline panel or by the authors of a systematic review is different from the available evidence regarding the population, intervention, comparator, or an outcome.

Parameter 4: Imprecision of results [dichotomous outcomes]

GRADE Working Group suggest downgrading the quality of evidence for any of the following three reasons:

total (cumulative) sample size is lower than the calculated “optimal information size” (OIS). OIS represents the number of patients generated by a conventional sample size calculation specifying a particular alpha and beta error, relative risk reduction, and baseline event rate.

total number of events is less than 300.

95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect includes both negligible effect and appreciable benefit or appreciable harm. GRADE suggests that threshold for "appreciable benefit" or "appreciable harm" that should be considered for downgrading is a relative risk reduction (RRR) or relative risk increase (Yost et al.) greater than 25%.

Parameter 5: Publication bias

Publication bias arises when investigators fail to report studies they have undertaken (typically those that show no effect). Methods to detect the possibility of publication bias in systematic reviews exist, although authors of the reviews must often guess about the likelihood of publication bias. A prototypical situation that should elicit suspicion of publication bias occurs when published evidence is limited to a small number of trials, all of which are showing benefits of the studied intervention.

The following abbreviations apply to all GRADE tables in Appendix H: ATP III LDL-c goals = Adult Treatment Panel low density lipoprotein cholesterol goals (of the National Cholesterol Education Program), OR = odds ratio, BAS = Bile acid sequestrants, CI = confidence interval, LDL-c = low density lipoprotein cholesterol, HC = hypercholesterolemia, CAD = coronary artery diseases, CHD = coronary heart diseases, T2DM = type 2 diabetes mellitus

Operationalization of Parameters

Parameters	Rated as NO limitation	Rated as SERIOUS limitation	Rated as VERY SERIOUS limitation
Limitation in design	Adequate allocation concealment Adequate blinding procedure Intention-to-treat analysis	Not all parameters were fulfilled, although some studies reported adequate allocation concealment or blinding or ITT	All parameters were unclear or inadequate
Inconsistency	No substantial heterogeneity (I- squared 50% or less) Populations in need of intensive treatment and subgroups Evidence-based on a single study	Not all parameters were fulfilled. For example, although analysis could be pooled for a common drug effect, populations were clinically diverse Analysis of various doses and statins were considered inconsistent	Diverse population and Substantial statistical heterogeneity
Indirectness	All studies were direct comparative trials Populations in need of intensive treatment and subgroups	Analysis of various statin doses Analysis in populations other than in need of intensive treatment or subgroups	Not used in the current review
Imprecision	95% confidence interval around the pooled data (or single estimate) was precise	Wide 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect and including both negligible effect and appreciable benefit or appreciable harm No events reported in a particular outcome If data not pooled and total number of events on evaluable participants were less than 300	Very wide 95% confidence interval (or alternative estimate of precision) around the pooled or best estimate of effect and including both negligible effect and appreciable benefit or appreciable harm
Publication bias	Evidence based in more than 10 trials with nonsignificant Egger's test	Evidence is limited to 10 or fewer trials limiting interpretation of publication bias	Evidence based in more than 10 trials with significant Egger's test for asymmetry
Parameters not used			
Limitation in design	Selective reporting outcome and/or other limitations – as it was not collected in our review		

Parameters not used	
Inconsistency	Outcomes were given the same strength, as we decided in 3 clinical outcomes and 1 surrogate outcome judge to be as relevant as the clinical outcomes
Indirectness	Outcomes were given the same strength, as we decided in 3 clinical outcomes and 1 surrogate outcome judge to be as relevant as the clinical outcomes
Imprecision	Total sample size being lower that the calculated OIS

Appendix F

Characteristics of excluded studies

Coogan 1996

Reason for exclusion	no assessment of shift or night work, no reference working group

Ekpanyaskul 2010

Reason for exclusion	no assessment of shift work, no reference working group

Elsner 1999

Reason for exclusion	Translator: no assessment of shift work

Enderlein 1998

Reason for exclusion	Translator: no assessment of shift work

Fritzsch 1979

Reason for exclusion	breast cancer not assessed

Geuskens 2011

Reason for exclusion	outcome is not BrCa incidence, but mortality and morbidity due to it

Gonthier 1991

Reason for exclusion	No assessment of shift work. No comparison group

Gunnarsdottir 1995

Reason for exclusion	**no assessment of shift work**

Gunnarsdottir 1997

Reason for exclusion	**no assessment of shift work**

Ji 2008

Reason for exclusion	**no assessment of shift work**

Kliukiene 1999

Reason for exclusion	**no assessment of shift work**

Kocic 1999

Reason for exclusion	**no assessment of shift work**

Kojo 2005

Reason for exclusion	**no assessment of shift work**

Labreche 2010

Reason for exclusion	**no assessment of shift work**

Li 2010

Reason for exclusion	**no assessment of shift work**

Lie 2007

Reason for exclusion	**no assessment of shift or night work, no reference working group**

Park 2012

Reason for exclusion	**no assessment of shift work**

Peplonska 2007

Reason for exclusion	**no assessment of shift work**

Petralia 1998

Reason for exclusion	**no assessment of shift work**

Petralia 1998a

Reason for exclusion	**no assessment of shift work**

Pollan 1999

Reason for exclusion	**no assessment of shift or night work, no reference working group**

Pukkala 2009

Reason for exclusion	**no assessment of shift or night work, no reference working group**

Rix 1996

Reason for exclusion	**no assessment of shift work**

Sankila 1990

Reason for exclusion	**no assessment of shift work**

van Wijngaarden 2001

Reason for exclusion	**no assessment of shift work, no reference working group**

Weiderpass 1999

Reason for exclusion	**no assessment of shift work**

Zeng 2007

Reason for exclusion	**no assessment of shift work**

Appendix G

Characteristics of studies awaiting classification

Chu 2010

Methods	case-control study
Participants	Taiwanese women coming for screening of breast cancer
Interventions	shift work
Outcomes	incident breast cancer
Notes	Unable to contact author to confirm methods, comparison and obtain data.

Grundy 2011

Methods	case-control study
Participants	female nurses from Vancouver, British Columbia
Interventions	Shift work
Outcomes	BrCa incidence
Notes	awaiting full text

Characteristics of on-going studies

Hansen 2013 a, b

Study name	unknown
Methods	unknown
Participants	women
Interventions	Shift work
Outcomes	Breast cancer incidence
Starting date	unknown
Contact information	Johnni Hansen <johnni@cancer.dk>
Notes	Author informed in personal communication that two studies will be published within the next year one similar to Hansen 2011and one prospective study.

Papantoniou 2011

Study name	Evaluation of breast cancer risk in relation to night-shift work in a case-control study in a Spanish population.
Methods	population case-control study
Participants	night working females
Interventions	shift work, compared to day work
Outcomes	Breast cancer incidence
Starting date	not known
Contact information	Castano Vinyals, Gemma <gcastano@creal.cat>
Notes	abstract from conference- contacted authors who advised to wait for full publication

Wang 2011

Study name	Studying night work and disease in the million women study
Methods	Cohort prospective- million women study
Participants	million women study cohort
Interventions	shift work compared to day work
Outcomes	Breast cancer incidence among others
Starting date	1996
Contact information	ruth.travis@ceu.ox.ac.uk
Notes	first publication with baseline characteristics of the cohort

Appendix H

Risk of Bias assessment for each included study

Study ID	Davis 2001
Exposuredefinition	High risk
Support for the judgment	Exposure was defined as beginning work after 7:00 PM and leaving work before 9:00 AM: only one of the aspects recommended by IARC
Exposure assessment	High risk
Support for the judgment	Subjective assessment. Reported by participants (interviews/questionnaires). Authors say: the exposure is based on an independent simple Job Exposure Matrix. Due to the nature of the study (registry based) such information (number of years of expsoure/ frequency of night work) was not available.
Blinding of assessors	Unclear risk
Support for the judgment	Not Reported
Reliability of exposure estimates	Low risk
Support for the judgment	Not clearly stated but both reviewers agreed it was implicit in description that same methods for cases and controls were used to measure exposure
Confounding	High risk
Support for the judgment	Only age and parity assessed.
Attrition	High risk
Support for the judgment	Over 20% non-response however did not differ between cases and controls
Analysis/research specific bias	High risk
Support for the judgment	Matching and conditional logistic regression used for analysis. However authors do not provide their considerations for the selection of the sample/ size. Dose response was not assessed adequately
Selective reporting	Low risk
Support for the judgment	Baed on methods we assume that estimates were presented for all tested hypotheses
Funding	Unclear
Support for the judgment	Although low risk because of a Non commercial funding source (grant R01CA55844 from the nationalcancer Institute). The role of the funding organization in study conduct is not reported.
Conflict of interest	Unclear

Support for the judgment	Not Reported

Study ID	**Hansen 2001**
Exposuredefinition	High risk
Support for the judgment	Women were considered to work predominantly at night if they had been employed for at least half a year in one or more of the trades in which at least 60% of the female responders had nighttime schedules. None of the aspects recommended for shift work assessment part of definition
Exposure assessment	High risk
Support for the judgment	Subjective classification of exposure to shift work: Information on the jobs of each case and control subject was converted into a job classification based on an extended version of the International Standard Industrial Classification of all Economic Activities, used to classify all companies in Denmark by the National Bureau of Statistics.
Blinding of assessors	Low risk
Support for the judgment	Correspondence: No- investigators assessing exposure were not aware of case or control status of the individual- the exposure was based on an independent simple Job Exposure Matrix.
Reliability of exposure estimates	Low risk
Support for the judgment	The employment histories of the control subjects were retrieved from the files of the pension fund in the same way as for cases.
Confounding	Low risk
Support for the judgment	'To adjust for socioeconomic status and reproductive factors (number of children, age at birth of first and last child), we estimated odds ratios (ors) and 95% confidence Intervals (cis) by conditional logistic regression analysis using the statistical package EPICURE.''
Attrition	Low risk
Support for the judgment	Register linkage used so non response did not occur
Analysis/research specific bias	High risk
Support for the judgment	The division of exposure was binary categorical, even though a dose analysis of sorts was done for a subgroup with 6 yrs or more of employment we do not consider it reflection of exposure.
Selective reporting	Low risk
Support for the judgment	Adjusted OR presented for the aim of 'assessing risk of Brca in women who worked predominantly at night'
Funding	Low risk
Support for the judgment	Study was not supported directly abu any organization, but indirectly since my salary was paid by the Danish Cancer Society
Conflict of interest	Low risk
Support for the judgment	No conflict of interest based on communication with author:

Study ID	**Hansen 2011**

Exposuredefinition	Low risk
Support for the judgment	Definition included at least two of the aspects recommended by IARC (shift duration, shift system)
Exposure assessment	High risk
Support for the judgment	Subjective assessment. Reported by participants (interviews/questionnaires)
Blinding of assessors	Low risk
Support for the judgment	Correspondence: No, in principle the interviewers were blinded to case-control status. Further, assessing a very objective measure such as shift-work should not be influenced by this. Finally, we didn't directly ask about shift work but rather about normal working time during a 'normal month' in each job.
Reliability of exposure estimates	Low risk
Support for the judgment	Not stated categorically but clear from report that same method of interview used for both groups
Confounding	Low risk
Support for the judgment	All major confounding factors/effect modifiers addressed. 3 (Age, BMI, Parity), were assessed in full. Of the remaining 2(ethnicity, SES), Ethnicity was considered not applicable and SES deemed similar among the groups based on extrenal data. Authors confirmed: 100% caucasian. Yes we have collected information on e.g education. But SES in itselt is only a crude indicator of potential confounders. Since we had been able to collect information on these there was no need to create a SES-variabel (althought we have data for that).
Attrition	High risk
Support for the judgment	Attrition differs between the groups (excluded from analysis13% cases, 16% controls) and has not been explained
Analysis/research specific bias	Low risk
Support for the judgment	Authors reported use of one or more methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring)
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypothesis tested as per aims
Funding	Low risk
Support for the judgment	'Unrestricted grants from the Danish Cancer Society and from the National Programme of Environmental Health Research. The funding sources did not involve in the data collection, data analysis, manuscript writing or publication.''
Conflict of interest	Low risk
Support for the judgment	Authors declare no conflict of interest

Study ID	Hansen 2012
Exposuredefinition	Low risk
Support for the judgment	Definition included 2 of the aspects recommended by IARC (shift duration/ shift time, shift system)
Exposure assessment	High risk
Support for the judgment	Subjective assessment. Reported by participants (interviews/questionnaires)
Blinding of assessors	Low risk
Support for the judgment	The trained telephone interviewers were blinded to case or control status
Reliability of exposure estimates	Low risk
Support for the judgment	Same method of interview used for both groups
Confounding	Low risk
Support for the judgment	All major factors assessed except SES which may well have been different between cases and controls considering its military. Authors communicated: Yes we have collected information on e.g education. But SES in itselt is only a crude indicator of potential confounders. Since we had been able to collect information on these there was no need to create a SES-variabel (althought we have data for that).
Attrition	High risk
Support for the judgment	Over 60 % non-response in both groups
Analysis/research specific bias	Low risk
Support for the judgment	Authors reported use of one or more methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring)
Selective reporting	Low risk
Support for the judgment	
Funding	Low risk
Support for the judgment	This study was supported by a grant from the Danish Ministry of Defence.The funding source had no role in the design or analysis of the study or in the decision to submit the manuscript for publication
Conflict of interest	Low risk
Support for the judgment	Authors declare no conflict of intrerest

Study ID	Menegaux 2012
Exposure definition	Low risk
Support for the judgment	Definition included 2 of the aspects recommended by IARC (shift duration/shift time, intensity)
Exposure assessment	High risk
Support for the judgment	Subjective assessment. Reported by participants (interviews/questionnaires)

Blinding of assessors	High risk
Support for the judgment	Correspondence: The interviewers were aware of The case-control status of The participants.
Reliability of exposure estimates	Low risk
Support for the judgment	Authors used same methods for cases and controls to measure exposure: A standardized questionnaire was used and interviewers were told to conduct the interview in the same way in both groups.
Confounding	Low risk
Support for the judgment	Adjusted for all major confounders: Adjusted for age, study area, parity, age at first full-term pregnancy, age at menarche, family history of breast cancer, current hormonal replacement therapy, body mass index, tobacco and alcohol. These quotas by SES were calculated from the census data available in each study area, to obtain a distribution by SES among controls identical to the SES distribution among general population women, conditionally to age. Ethnicity was all white.
Attrition	Low risk
Support for the judgment	Reported for both cases and controls and did not differ in size and reasons 21% and 24%
Analysis/research specific bias	Low risk
Support for the judgment	Authors reported use of more than one methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring)
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypothesis tested as per aims
Funding	Low risk
Support for the judgment	Grant sponsor: Agence Nationale de s_ecurit_e sanitaire de l'alimentation, de l'environnement et du travail (ANSES); Grant number: 2010/2/2073; Grant sponsors: Agence Nationale de laRecherche (anot Reported); Fondation de France; Institut National du Cancer (INCA); Ligue contre le Cancer Grand Ouest; Association pour le recherche contre le cancer (ARC). The sponsors had no role in the conduct of the study, except funding! A final report was provided to them at the end of the contract and validated by a scientific committee.
Conflict of interest	Low risk
Support for the judgment	- There is no conflict of interest to disclose.

Study ID	**Lie 2006**
Exposure definition	High risk
Support for the judgment	No clear definition provided. Definition of exposure is categorical with an arbitrary threshold (Job at infirmary) which covers only one of the recommended aspects of exposure (duration of work at job assumed to have night work exposure).
Exposure assessment	High risk
Support for the judgment	Jobs were categorized by authors into exposures: ''Work history from the nurse registry was self-reported...In order to calculate number of years of night work out of total work time as a nurse, some assumptions had to be made. Imputation around the 1970 census was mainly based on work history from the last update of the nurse register in 1968.'' authors elaborated in correspondence:The 2006-study includes cases diagnosed from 1960 to 1982 (and matched controls). The work history we applied in that study came from two registers:

	1)the Norwegian Board of Health's registry of all nurses, including work sites (years, site, department), however no information on schedules or night work. 2) Information from 3 censuses (work and industry codes), no information on night work As we had no information about work schedules or frequency of night-shifts in that study, we used a crude exposure metric for night work: cumulative number of years worked in hospitals or other 24-hour institutions.
Blinding of assessors	High risk
Support for the judgment	Exposure data were coded by researchers into categories after the cases and controls were identified and matched
Reliability of exposure estimates	Low risk
Support for the judgment	The authors did not state that the same methods were used to measure exposure risk factors in cases and controls. Report implies linkage was established between cancer cases and the nurses registry before the job categories byExposurewere defined.
Confounding	High risk
Support for the judgment	All major confounders Age, Parity, SES, were not satisfactorily assessed: ethnicity not an issue: The cohort is ethnically quite homogeneous, most of them ethnical Norwegians. A very small proportion of nurses came from other countries, mainly from Denmark and Sweden. Correspondence: The work history in the 2006-study, which was based on two registers, does not include information on BMI, which was therefore not adjusted for. Since its the same cohort we can assume the BMI to have the same effect as in 2011 study. Self-reported data for confounding factors from health care databases.
Attrition	Low risk
Support for the judgment	Register linkage used so nonresponse did not occur
Analysis/research specific bias	Low risk
Support for the judgment	Adjustment in multivariate model, and sensitivity analyses. Dose response (increasing exposure in 5 and 10 yr categories) assessed in analysis. Sample size calculation not provided no justification given
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for the hypotheses tested as per aims
Funding	Low risk
Support for the judgment	Noncommercial funding source (Norwegian Women's Public Health Association). Source had no influence on study conduct.
Conflict of interest	Low risk
Support for the judgment	No conflict of interests to be declared

Study ID	**Lie 2011**
Exposure definition	Low risk
Support for the judgment	Definition included two of the aspects recommended by IARC (shift duration, shift system)
Exposure assessment	High risk
Support for the judgment	Subjective assessment. Reported by participants (interviews/questionnaires)
Blinding of assessors	Low risk
Support for the judgment	Interviewers were blind to case status

Reliability of exposure estimates	Low risk
Support for the judgment	Implicit even though not stated as investigators were blind to case status so likely that identical interviews for both cases and controls were carried out
Confounding	Low risk
Support for the judgment	Although only age and parity adjusted estimates presented, authors did assess all other major confounders and only included the ones in analysis which changed the results by more than 10%. Ethnicity has not been assessed but likely a low percentage of nonwhite nurses... Author confirmed: The cohort is ethnical quite homogeneous, most of them ethnical Norwegians. A very small proportion of nurses came from other countries, mainly from Denmark and Sweden.• The work history in the 2011-study is based on a telephone interview, and also includes information about height and weight, at age 18 years and at the time of diagnosis/reference. BMI (at 18 and at time of diagnosis) were not included in the final model, as it did not seem to be a confounder.
Attrition	High risk
Support for the judgment	Variation in non-response by group, reasons not provided. Total non-response over 30%. Potential differential bias might have been introduced by the exclusion of the deceased cases.
Analysis/research specific bias	Low risk
Support for the judgment	Authors reported use of one or more methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring). Dose response assessed in analysis. No justification or calculation for sample size provided in report
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Low risk
Support for the judgment	Noncommercial funding source (Research Council of Norway (contract 185776/V50) and by grants from the South-Eastern Norway Regional Health Authority (3b-107) and the Norwegian Cancer Society (PK01-2009-0444). Source had no influence on study conduct.
Conflict of interest	Low risk
Support for the judgment	Authors declare no conflict of intrerest

Study ID	**O'Leary 2006**
Exposuredefinition	High risk
Support for the judgment	Definition covers only one aspect of exposure (start or end time of shift)
Exposure assessment	High risk
Support for the judgment	Subjectively measured: Reported by participants (interviews/questionnaires)
Blinding of assessors	Unclear risk
Support for the judgment	Not Reported
Reliability of exposure estimates	Low risk
Support for the judgment	Same methods (EBCLIS interview) for cases and controls to measure exposure

Confounding	High risk
Support for the judgment	Age and parity assessed
Attrition	Low risk
Support for the judgment	Non response was reported for both cases(13%) and controls(16%) and did not differ in size and reasons
Analysis/research specific bias	Unclear risk
Support for the judgment	Authors reported use of one or more methods to reduce bias (standardization, matching, adjustment in multivariate model, stratification, propensity scoring). Dose response assessed in analysis. No justification or calculation for sample size provided in report
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Unclear risk
Support for the judgment	Although low risk because of Noncommercial funding sources (grant CA/ES 62991 from the National Cancer Institute/National Institute of Environmental Health Sciences (NIEHS) (EBCLIS Group); grant ES11659 from NIEHS (Dr. Richard Stevens); grant CA/ES 66572 from the National Cancer Institute/NIEHS (LIBCSP); and grant P30ES10126 from NIEHS (Dr. Marilie Gammon).)
Conflict of interest	Low risk
Support for the judgment	Authors declare no conflict of interest

Study ID	**Pesch 2010**
Exposure definition	High risk
Support for the judgment	Definition covers only one aspect of exposure (start or end time of shift)
Exposure assessment	High risk
Support for the judgment	Subjectively measured: Reported by participants (interviews/questionnaires)
Blinding of assessors	Low risk
Support for the judgment	Correspondence: Due to the study design it is not possible for interviewers not to realize case-control status (interviews were performed with incident breast cancer patients).
Reliability of exposure estimates	Low risk
Support for the judgment	The authors used same methods for cases and controls to measure exposure
Confounding	Low risk
Support for the judgment	Major confounding factors/effect modifiers (Age, BMI, Ethnicity, Parity (number of children, age at first birth, and education(for SES)) were assessed in full.
Attrition	High risk
Support for the judgment	% of nonresponse differed among cases (12%) and controls (33%)
Analysis/research specific bias	Low risk

Support for the judgment	Corrected for a potential selection bias using a resampling and bootstrapping procedure with logistic regression models conditional on age in 5-year groups, adjusted for family history of breast cancer, hormone replacement use, and number of mammograms. Dose response assessed in analysis. .
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Low risk
Support for the judgment	study funded by Noncommercial organizations (German Federal Ministry of Education and Research (BMBF) grants 01KW9975/5, 01KW9976/8, 01KW9977/0, 01KW0114, and 01KH0411, the Research Institute of Occupational Medicine of the German Social Accident Insurance (BGFA), the ert Bosch Foundation of Medical Research, the Evangelische liniken (Evangelical Clinic) Bonn gmbh, and the Deutsches Krebsforschungszentrum (German Cancer Research Center)) Correspondence: sponsors of the study did not have any role in the conduct of the study.
Conflict of interest	Low risk
Support for the judgment	Correspondence: No conflict of interest

Study ID	**Pronk 2010**
Exposure definition	Low risk
Support for the judgment	Definition included 2 of the aspects recommended by IARC (shift duration: number of years, shift Intensity)
Exposure assessment	High risk
Support for the judgment	Subjectively measured: Reported by participants (interviews/questionnaires) and proxy used to allocate exposure status (job matrix, job title)
Blinding of assessors	Low risk
Support for the judgment	Occupational histories were obtained prior to cancer diagnosis and assignment of night-shift work was conducted without knowledge of case status
Reliability of exposure estimates	Low risk
Support for the judgment	Correspondence: cases and controls exposure assessed in the same manner
Confounding	Low risk
Support for the judgment	Adjusted for Age, education, family history of breast cancer, number of pregnancies, age at first birth, occupational physical activity. BMI assessed but not controlled for as it had no effect on results and ethnicity was likely not varied. Education as proxy for SES (correspondence)
Attrition	Low risk
Support for the judgment	7% total loss even though group-wise loss Not Reported
Analysis/research specific bias	Low risk
Support for the judgment	'Cox proportional hazards regression (PROCPHREG) with age as the time scale and stratification by birth cohort (5-year intervals). Since the self-reported information on night-shift work was obtained during the second follow-up, this analysis was restricted to person-years and cases with incident

	breast cancer diagnosed after the second follow-up (n = 69,982, of whom 69,472 provided information on night-shift work)''. Dose response analysed. Sample size justification was not clearly stated, not really... However, authors elaborate all decisions regarding restricting the sample and why they did it.
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Unclear risk
Support for the judgment	Although study funded by Noncommercial (US National Institutes of Health (grant R01 CA70867) and the Intramural Research Program of the National Institutes of Health (contract N02 CP1101066)) organizations the role of these is not reported in study conduct. Correspondence: I am not sure about this. You could contact my former colleagues in the cc if you want to find out
Conflict of interest	Low risk
Support for the judgment	Authors declare no conflict of interest

Study ID	**Schernhammer 2001**
Exposure definition	High risk
Support for the judgment	Did not consider the permanent night-shiftworkers who, "being not rotating were included in the control group", as the authors themselves explained (personal communication). Moreover the question was asked (by a mail questionnaire) only once during the the whole period of observation
Exposure assessment	High risk
Support for the judgment	Mail Questionnaire once only. Authors explained that unless self-reported data on work cannot be collected from logs in the US legally. Thus this is a matter out of their control and may be US studies should be considered separately for assessment risks.
Blinding of assessors	Low risk
Support for the judgment	Confirmed with authors prospective allocation of exposure
Reliability of exposure estimates	Low risk
Support for the judgment	Intra-observer variability is reported by means of a subjective judgment of reliability:'' it is likely that our results are accurate, because other self-reports have been highly accurate in this cohort (47), and previous validations of similar questions (e.g., electric blanket use) (48) have shown reasonable reproducibility.'' authos clarified in communication that reliability can't be tested as its not legal to track nurses data unless they self-report in the US. But they measured it for electric blanket use for both studies which was found consistent.
Confounding	Low risk
Support for the judgment	Age, BMI, SES, Parity, Age at menarche; age at menopause; age at first birth; alcohol consumption; oral contraceptive use; use of postmenopausal hormones; menopausal status; benign breast disease; family history of breast cancer; Regarding ethnicity and SES author replied:the NHS cohorts are very uniform with over 95% of all women being white/Caucasian.
Attrition	Low risk
Support for the judgment	Groupwise loss not reported however total loss is less than 10% for a very large cohort

Analysis/research specific bias	Low risk
Support for the judgment	Authors reported use of one or more methods (Pooled logistic regression models) to reduce bias. Increasing duration of exposure assessed in 10 yr categories as supgroup analyses.
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Low risk
Support for the judgment	Supported by Public Health Service grants CA/ES62984 (National Cancer Institute [NCI]/National Institute of Environmental Health Sciences) andCA87969 (NCI), National Institutes of Health, Department of Health and Human Services. E. S.Schernhammer was supported in part by a Research Grant in Cancer Prevention from the Austrian FederalMinistry of Education, Science and Culture. Confirmed with authors low risk no involvement of the funder
Conflict of interest	Low risk
Support for the judgment	Confirmed with authors there are no conflicts of interest.

Study ID	**Schernhammer 2006**
Exposuredefinition	High risk
Support for the judgment	Did not consider the pernanent night-shiftworkers separate from rotators. ''Years worked rotating night-shifts with at least three nights per month in addition to days or evenings in that month", and "permanent night-shifts for 6 or more months"
Exposure assessment	High risk
Support for the judgment	Mail Questionnaire repeated 4 times
Blinding of assessors	Low risk
Support for the judgment	Confirmed with authors prospective allocation of exposure
Reliability of exposure estimates	Low risk
Support for the judgment	
Confounding	Low risk
Support for the judgment	Age, BMI, Parity, SES, Ethnicity. Age at menarche; age at menopause; age at first birth; alcohol consumption; oral contraceptive use; use of postmenopausal hormones; menopausal status; benign breast disease; family history of breast cancer; Regarding ethnicity and SES author replied:the NHS cohorts are very uniform with over 95% of all women being white/Caucasian. SES adjustment was done for husbands' educational attainments as the proxy for SES, since we have no other good indicators of SES. Also because they are all nurses, there is relatively little variation in SES in our cohorts.
Attrition	Low risk
Support for the judgment	Differential loss is not reported and unlikely as total loss is under 1%
Analysis/research specific bias	Low risk
Support for the judgment	Same as NHS I (Schernhammer 2001)
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Low risk

Support for the judgment	Supported by Public Health Service grants CA/ ES62984 (National Cancer Institute [NCI]/NationalInstitute of Environmental Health Sciences) and CA87969 (NCI), National Institutes of Health,Department of Health and Human Services. E. S. Schernhammer was supported in part by a Research Grant in Cancer Prevention from the Austrian Federal Ministry of Education, Science and Culture. Confirmed with authors low risk no involvement of the funder
Conflict of interest	Low risk
Support for the judgment	Confirmed with authors there are no conflicts of interest.

Study ID	**Schwartzbaum 2007**
Exposuredefinition	High risk
Support for the judgment	Definition is largely based on proportion of ppl usually involved in night-shift work in an occupation. A job exposure matrix of sorts prone to bias and missclassification of exposure liekly, as indicated by authors as well
Exposure assessment	High risk
Support for the judgment	Previously recorded data from survey of living conditions (interviews in 1977-1981) was used: ''Information about work schedules in different occupations within specific industries was obtained from the annual Survey of Living Conditions (ULF) conducted byStatistics Sweden during 1977–1981. Over these years, altogether 55 323 persons were randomly selected fromthe Swedish population, and 46 438 (84%) participated in personal interviews conducted by specifically trained interviewers. The participants answered questions abouttheir usual occupation and workhours [eg, daytime,evening and night hours, rotating shift work with twopossible shifts per day, rotating shift work with three ormore possible shifts per day (“three-shift” schedule), orvarying timetable]. Working a rotating shift with threeor more possible shifts per day usually entails alternating daytime and nighttime workhours. Furthermore, theparticipants were asked to give information about whenthey started and ended working each day during theweek preceding the interview''…….Thus the job-exposure matrix that we constructed contained information about the percentage of shiftworkers in each job title and industry combination and was linked to the census data obtained for each personin the cohort. In our analyses, we classified, as shiftworkers, people working in job-title and industry combinationswith at least 40% shift workers.
Blinding of assessors	Low risk
Support for the judgment	Correspondence: Exposure data was collected completely independent from case status of the participants.
Reliability of exposure estimates	High risk
Support for the judgment	Correspondence: We did not use expert assessments to determine exposure (exposure assessors), so kappa estimates are not relevant in the context of the exposure assessment used in our study. The exposure assessment was based on a very large survey (almost 50 000 persons) randomly selected from the Swedish population (with high response rate) that were asked about their working hours and occupational title and industry.
Confounding	High risk
Support for the judgment	Only two of the major confounding factors adjusted for (age and SES). Correspondence: We did not have information about BMI

	or parity. But I believe that adjusted and unadjusted risk estimates in studies that did have information about e.g. Parity did not differ from each other, so these confounders did not seem to have an effect on risk estimates.
Attrition	High risk
Support for the judgment	Participants were not followed as data about them cross linked between registers. Authors report no info on any missing data and hence excluded ones. However original survey had 16% non response.
Analysis/research specific bias	High risk
Support for the judgment	Authors used multivariate model adjustment for major confounders, and assumption also made clear. They performed sensitivity and subgroup analyses to test their assumptions as well. But the starting point (the exposure assesment) was too crude (both in terms of work sectors examined (admitted by the authors themselves) and as cut-off percentages) so that the sophisticated statistical analysis cannot compensate. Plus the sample was based on a random selection from census. So, in general terms, we believe the risk is high.
Selective reporting	Low risk
Support for the judgment	Authors state: ''The primary purpose of our present study was to expand research on the association between shift work and cancer by looking at cancer risks at many sites among both male and female night and rotating shift workers in a large occupational cohort.'' but do not present rotating and night-shift work separately and also do not present some of the analyses done with varying definitions of shift work. Stating the results were almost the same.
Funding	Low risk
Support for the judgment	The study was funded by a Swedish research council that was not involved in the conduct of the study.
Conflict of interest	Low risk
Support for the judgment	Confirmed with authors there are no conflicts of interest.

Study ID	**Tynes 1996**
Exposuredefinition	High risk
Support for the judgment	Definition of exposure/ case is categorical with an arbitrary threshold (e.g.1 yr or more, ever done night work. Also the definition is not exclusive to shift work but includes additional exposures to some extent)
Exposure assessment	High risk
Support for the judgment	Proxy used to allocate exposure status (job matrix, job title) . In this case ships were classified intoExposurecategories ''exposure classification of Norwegian merchant ships''
Blinding of assessors	High risk
Support for the judgment	Authors state'' For cases and controls drawn from the TC, detailed job histories on ships were collected. Shift work (categories 0,1,2,3) and travel through time zones (categories 0,1) were classified for each ship mentioned in the job histories by a shipping journalist and a researcher with detailed knowledge of the recent history (1945-90) of Norwegian merchant ships. '' indicating case and control status were known before exposure metrics were collected.
Reliability of exposure estimates	Unclear risk
Support for the judgment	Exposure estimate was mad “a posteriori” by two people not directly involved with this job. No indication that reliability was

	assessed in report.
Confounding	High risk
Support for the judgment	Authors say in text that fertility factors and age were assessed, aparently from tables, none of theses factors have been adjusted for, the only adjustment is subgroup results reported by age for under and over 50 yrs and a statement that adjusted OR refer to adjustment for employment duration for shift work estimates. Author explained in correspondence that they don't have access to the data any more.
Attrition	Low risk
Support for the judgment	For cohort the nonresponse is low (TC: 5.4%) Not Reported for nested case-control but unlikely any additional
Analysis/research specific bias	High risk
Support for the judgment	Authors state that they used fertility categories for confounding estimation (For case-control women born 1935 and later, fertility data was available and confounding from such factors was evaluated by including a fertility variable with three categories (1 =no children; 2 = first child born at age 25 years and over; 3 = first child born before age 25) but tables indicate only employemnt duration was adjusted for and its something they do not explain. No dose assessment, unclear how sample was decided.
Selective reporting	High risk
Support for the judgment	Aims and objectives inconsitent between abtsract and report and results are not a reflection of these completely. Shift work was only one of the exposures they aimed to assess. However authors do not report results on the other exposures they aimed to assess, EMF and RF. Similarly, the title indicates breast cancer only, abstract indicates EMF as a primary cause of breast cancer, however SIR on all cancers for telecom operators is reported for shift work.
Funding	Low risk
Support for the judgment	Liekly no funders. Report acknowledges Norwegian Telecom and the Central Bureau of Statistics for valuable cooperation; Oddvar Sandvin for help with computing and analysis; Dag S. Bakka for help with exposure classification of Norwegian merchant ships; Dr Richard Stevens for his thoughtful review of the manuscript; and Kirsten Bolstad for details on the work of radio and telegraph operators at sea.
Conflict of interest	Unclear risk
Support for the judgment	Not reported.

Study ID	**Knutsson 2012**
Exposuredefinition	High risk
Support for the judgment	Although the WOLF questionnaire is quite detailed the definition of night-shift worker is simply: If the data indicated shift work with night work on ≥1 occasion, and day work or shift work without night for the rest, the participant was regarded as a worker with night-shift work.
Exposure assessment	High risk
Support for the judgment	''In order to categorize the participants in three groups (ie, day work and shift work with and without night shifts), we used data from baseline, follow-up in 2000–2003 (WOLFF), and follow-up in 2009 (WOLFU). If data indicated day work on all occasions when the subject participated, she was regarded as a day worker. If data indicated shift work without night work on ≥1 occasion, and day work for the rest, the participant was defined as a worker with shift work without night work. If the data indicated shift work with night work on ≥1 occasion, and day work or shift work without night for the rest, the

	participant was regarded as a worker with night-shift work.'' Comment: subjective allocation of exposure based on available data, even though the questionnaire was detailed the components have not been used in assessing exposure levels.
Blinding of assessors	Unclear risk
Support for the judgment	Correspondence: "This is a prospective, longitudinal cohort study. Ït is not a case-control study. Therefore data on exposure were collected before the participants were diagnosed with cancer. Data on all participants, who entered the study at baseline were checked in the cancer registry at follow-up." Comment: statement does not apply to blind assessment. Although data collected prospectively allocation to exposure is retrospective and likely data driven in our opinion."
Reliability of exposure estimates	Unclear risk
Support for the judgment	Correspondence: We have reported on that (reliability) in the article (mentioned both in methods and the discussion). In report: The agreement between information given at baseline and follow-up, however, was better when considering shift work with night-shifts. Of those who reported no experience of night-shift work at follow-up, only 2% reported night work at baseline. It appears that retrospective information about night-shift experience is more reliable than information about shifts without night work. In 53% of the subjects, we had retrospective information about lifetime exposure to shift work (with and without night work), in 36% we had only baseline information. The baseline question-naire provided information only on current shift work/night work, and it is probable that some subjects, who were classified as day workers based on this information only, were actually former shift workers. However, it is not possible to draw any conclusions about how this misclassification could have biased our results. Comment: subjective assessments not corroborated by data. 36% had only baseline info and only 2% reported night-shift at baseline. Report acknowledges misclassification potential and reliability of estimates remains in question.
Confounding	Low risk
Support for the judgment	BMI, Parity, SES, Ethnicity. Correspondence: ''The number of subjects, who were born in another country than Sweden, was 424. We considered that number so small (<10%), that we decided not to control for that variable. We have adjusted for age in the cox regression model. This is described in the method section.''
Attrition	High risk
Support for the judgment	Correspondence: Breast cancer and death were the only reasons for drop out.The number or drop-outs with respect to cancer is zero. All participants at baseline have been compared with the data in the Swedish Cancer Registry. The number of drop-outs with respect to answering the questionnaire in 2009 is as suggested by you (60%).
Analysis/research specific bias	High risk
Support for the judgment	No dose response
Selective reporting	Low risk
Support for the judgment	Adjusted estimates presented for all hypotheses tested as per aims
Funding	Low risk
Support for the judgment	We got a small funding from a local hospital fund for cancer research (4500 dollars). - They did not take part in planning of conducting the study. The just asked for a final report.
Conflict of interest	Low risk

Support for the judgment	No conflict of interests identified

Study ID	**Li 2011**
Exposuredefinition	Low risk
Support for the judgment	Definition included 2 of the aspects recommended by IARC (start and end time/duration, shift system)
Exposure assessment	Low risk
Support for the judgment	Prospectively collected factory data for shift work were used for exposure
Blinding of assessors	Unclear risk
Support for the judgment	Not reported
Reliability of exposure estimates	Low risk
Support for the judgment	Same methods were used for data collection for all participants by trained field workers
Confounding	Unclear risk
Support for the judgment	Age and parity assessed according to report, ethnicity entirely Chinese, SES may be similar in factory workers. BMI unknown. Awaiting communication from authors.
Attrition	Low risk
Support for the judgment	For the nested case-control part of the study the loss is less than 1% for cases and controls each
Analysis/research specific bias	Low risk
Support for the judgment	Cox proportional hazards modeling, adapted for the stratified case-cohort design to calculate relative risk estimates (hazard ratios [hrs] and 95% confidence intervals [cis]) for breast cancer associated with various measures of night-shift work. Subgroup and dose response analyses conducted.
Selective reporting	Low risk
Support for the judgment	Thesis available. All aims assessed
Funding	Unclear risk
Support for the judgment	Part of a grant funded project, we dont have communication from authors to confirm that the funding body has any role. Though unlikely as it is purely academic research (phd thesis)
Conflict of interest	Unclear
Support for the judgment	We dont have communication from authors to confirm that the funding body has any role. Though unlikely as it is purely academic research (phd thesis)

Supplements:

1. Author provided data

Study ID	**Authors correspondence - unpublished information** Provided kindly by: Schernhammer E., Rabstein S., Pronk A., Tynes T., Knutsson A., Hansen J., Guenel P, Lie J-A S., Feychting M.
Hansen 2001	• Sponsor: No not directly, but indirectly since my salary was paid by the Danish Cancer Society. • No (assessor aware of case status) – the exposure is based on an independent simple Job Exposure Matrix. • All information in the study is taken from available registry data about one year before submission. • No. Due to the nature of the study (registry based) such information (number of years and/ or frequency in shift work) was not available.
Hansen 2011	• The interviewers were blinded to case-control status. Further, assessing a very objective measure such as shift-work should not be influenced by this. Finally, we didn't directly ask about shift work but rather about normal working time during a 'normal month' in each job. • 100% caucasian. We have collected information on e.g education. Since we had been able to collect information on these there was no need to create a SES-variable (although we have data for that). • We had a response rate of about 90% in both cases and controls
Hansen 2012	• Assessments for socioeconomic status: we have collected information on e.g education. But SES in itself is only a crude indicator of potential confounders. Since we had been able to collect information on these there was no need to create a SES-variable (although we have data for that). • 100% were Caucasians. • Reasons for nonresponse: We don't know the answer beyond the normal reasons for this potential problem. We have actually discussed the consequences of differential non-response in the text.
Menegaux 2011	In our population-based case-control study, the selection of population controls was made carefully in order to avoid selection bias, and to obtain a representative sample of the study base. There were 109 women (4.4%) who had never been employed (36 cases and 73 controls). Study results were unchanged when never working women were excluded from the analyses. - The interviewers were aware of the case-control status of the participants. A standardized questionnaire was used and interviewers were told to conduct the interview in the same way in both groups. - The sponsors had no role in the conduct of the study, except funding! A final report was provided to them at the end of the contract and validated by a scientific committee. - There is no conflict of interest to disclose. Based on info from supplemental data ethnicity was only white
Lie 2006 **Lie 2011**	Both the 2006- and the 2011 studies of Norwegian nurses are case-control studies nested within the same cohort of nurses. However, the 2011 study is not an update of the 2006 study. The 2006-study includes cases diagnosed from 1960 to 1982 (and matched controls). The work history we applied in that study came from two registers: 1) the Norwegian Board of Health's registry of all nurses, including work sites (years, site, department), however no information on schedules or night work. 2) Information from 3 censuses (work and industry codes), no information on night work As we had no information about work schedules or frequency of night-shifts in that study, we used a crude exposure metric for night work: cumulative number of years worked in hospitals or other 24-hour institutions. A main objective of the 2011 study was to obtain data of better quality, concerning work history and night work, but also concerning potential confounders. To obtain this, we conducted telephone interviews, of all cases diagnosed with breast cancer between 1990 and 2007, alive at the time of the interview in 2009, and frequency matched controls. The nurses were interviewed about each job held as a nurse, whether it included night-shifts, and if yes, the average number of night-shifts per month and the number of consecutive night-shifts. In the 2011 study we also included analyses applying the same exposure metric as in the 2006-study (cumulative number of years worked in institutions). In contrast to the elevated risk seen in 2006, no increased risk was found in 2011, when using this metric. A contributing factor for this discrepancy of results, may be that exposure to night work has decreased over the relevant period (2006 study cases were diagnosed 1960-1982, 2011 study-cases were diagnosed 1990-2007). We did not adjust for socioeconomic status or ethnicity in any of the two studies. The cohort is ethnical quite homogeneous, most of them ethnical Norwegians. A very small proportion of nurses came from other countries, mainly from Denmark and Sweden. • The work history in the 2006-study, which was based on two registers, does not include information on BMI, which was therefore not adjusted for.

	• The work history in the 2011-study is based on a telephone interview, and also includes information about height and weight, at age 18 years and at the time of diagnosis/reference. BMI (at 18 and at time of diagnosis) were not included in the final model, as it did not seem to be a confounder. In our 2011-study, 19.9 years (≈ 20 years) was the mean duration of work in schedules including night-shifts in the open category of 12+ years. In our study from 2006 there were only 24 subjects in the 30+ year category, and maximum number of years with night work was 42.0 years. I guess the median was approximately 36 years.
Schernhammer 2001 **Schernhammer 2006**	The NHS cohorts are very uniform with over 95% of all women being white/Caucasian. As far as SES adjustment is concerned - are you referring to the nurses' or their husbands' educational attainments (the proxy we sometimes use for SES, since we have no other good indicators of SES)? Also, keep in mind that, because they are all nurses, there is relatively little variation in SES in our cohorts. We used a full cohort approach, not a case-control study design. Author also provided unpublished frequency distribution data in their sample: 'Firstly, you may find this small pilot study which we conducted in NHS2 a while ago, rather reassuring as far as your estimation for average number of nights/mo is concerned, and perhaps you want to use this pilot data to support your choice: From a small pilot study of approximately 60 women from within the NHS2 cohort (unpublished data), we know that there is a relatively large spread of number of nights worked: among rotating night workers, the average number of nights worked per month was 6.4 (SD, 4.1) with a range from 1 to 21 nights per month, whereas among permanent night workers, the average number of nights worked per month was 12.3 (SD, 4.8) with a range from 3 to 30 nights per month. Secondly, when looking at the tables and proposed numbers you sent upfront, - I generally agree with your estimates; I would advice, however, to be equally conservative with your estimate for the average duration of shift work in years in the highest groups in both cohorts; for 30+ years of shift work, I would propose to use 30 years, and not 43 years; likewise, in NHS2, I would use 20 years, and not 28 years. This is most consistent with your otherwise always (in my view very wisely chosen) conservative approach and if you pick the average duration as 43 and 28 years in these upper categories, they may let any p for trend appear significant as they artificially pull the tail of this variable. In our own publications, we have chosen this conservative approach (coding the upper categories as 30 and 20 years, respectively, when we calculated p for trends), so it would also be consistent with us.'
Schwartzbaum 2007	• The study was funded by a Swedish research council that was not involved in the conduct of the study. • Reliability estimates for the exposure assessors/ assessments We did not use expert assessments to determine exposure (exposure assessors), so kappa estimates are not relevant in the context of the exposure assessment used in our study. The exposure assessment was based on a very large survey (almost 50 000 persons) randomly selected from the Swedish population (with high response rate) that were asked about their working hours and occupational title and industry. • The authors have no conflicts of interest. • As described in the paper, we have information about the occupation held at the 1960 and 1970 censuses, but we have no information in between the censuses (the 1965 year census did not include occupational information). Therefore we cannot provide duration in 5 year categories. Exposure assessment was made in a similar way as in the first Danish paper about shift work. Exposure was not assessed for each individual person, but for an occupational title. In the paper we write: "Information about work schedules in different occupations within specific industries was obtained from the annual Survey of Living Conditions (ULF) conducted by Statistics Sweden during 1977-1981." These are interview based surveys made with 46 438 participants, who answered questions about their usual occupation and workhours. Our goal was to identify occupations in which a large proportion of workers had workhours that could affect melatonin levels, i.e. Workhours during the night. From the ULF survey we identified combinations of occupation and industry where a large proportion of the workers had workhours including night work. We analyzed cancer risk in occupation-industry combinations where at least 40% were shift workers according to our definition (i.e. Included night work), and also combinations where at least 70% were shift workers. Duration of exposure to shift work was taken into consideration by analyzing cancer risk in persons who had an occupation-industry combination defined as shift work in both the 1960 and the 1970 censuses. • Blind to the case status Exposure data was collected completely independent from case status of the participants. • Confounders We did not have information about BMI or parity. But I believe that adjusted and unadjusted risk estimates in studies that did have information about e.g. Parity did not differ from each other, so these confounders did not seem to have an effect on risk estimates.
Tynes 1996	Explained in correspondence that they didn't have access to the data any more so were unable to help.
Knutsson	- We got a small funding from a local hospital fund for cancer research (4500 dollars). - They did not take part in planning or conducting the study. The just asked for a final report. - No conflict of interests identified. - This is a prosective, longitudinal cohort study. Ït is not a case-control study. Therefore data on exposure were collected before the participants were diagnosed with cancer. Data on all participants, who entered the study at baseline, were checked in the cancer registry at follow-up.

	- We have reported on that (reliability of exposure estimates) in the article (mentioned both in methods and the discussion). - Breast cancer and death were the only reasons for drop out. The number or drop-outs with respect to cancer is zero. All participants at baseline have been compared with the data in the Swedish Cancer Registry. The number of drop-outs with respect to answering the questionnaire in 2009 is as suggested by you (60%).
Pesch 2010	-Due to the study design it is not possible for interviewers not to realize case-control status (interviews were performed with incident breast cancer patients). -No, the sponsors of the study did not have any role in the conduct of the study. -There is no conflict of interests. statistics for the highest night exposure groups of our GENICA shift work population: Cumulative lifetime night-shift exposure (highest exposure group), cases: Max= 6695, mean = 2118, median = 1607 Cumulative lifetime night-shift exposure (highest exposure group), controls: Max = 5915, mean= 2094, median =1655 Number of Years with night-shift above 20 years, cases: Max = 35 years, mean = 27.3, median = 27.8 Years of night-shift above 20 years, cases: Max = 29 years, mean 25.5, median = 26.5
Pronk 2010	Assignments of exposure status carried out in the same way for cases and controls? Yes they were Assessment of socioeconomic status: We have used education level to adjust for socioeconomic status. There may have been other potential proxies as well, but I don't remember exactly all the variables. Role of sponsors in the conduct of the study? I am not sure about this. You could contact my former colleagues in the cc if you want to find out. Also, the study report does not indicate any potential conflict of interests. Should we assume that none exist? There were no conflicts of interest. Open ended Exposure category: This question is a little harder to answer. I would need the data for that and I do not have access not the dataset anymore.

2.

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