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Night work and breast cancer risk: A systematic review and meta-analysis

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Abstract

The association between occupations that involve night shift work (a surrogate for exposure to light at night with subsequent melatonin suppression) and breast cancer risk is uncertain. We therefore conducted a systematic review and meta-analysis of observational studies to assess the effects of night work on breast cancer risk.

Data sources were MEDLINE from January 1960 to January 2005, experts in the field, bibliographies, and abstracts. Search terms included night work terms, flight personnel terms, cancer terms, and risk terms. Independent data extraction by two authors using standardised forms was performed. The method of DerSimonian and Laird was used to derive combined estimates and Egger's; and Begg and Mazumdar's tests for publication bias were conducted.

Based on 13 studies, including seven studies of airline cabin crew and six studies of other night shift workers, the aggregate estimate for all studies combined was 1.48 (95% CI, 1.36–1.61), with a similar significant elevation of breast cancer risk among female airline cabin crew (standardised incidence ratio (SIR), 1.44; 95% CI, 1.26–1.65), and female night workers (relative risk (RR), 1.51; 95% CI, 1.36–1.68) separately. We found some evidence suggesting confounding due to incomplete adjustment for breast cancer risk factors, with smaller effects in the studies that more completely adjusted for reproductive history and other confounding factors. Egger's and Begg and Mazumdar's tests for publication bias showed no significant asymmetry (P > 0.05).

Studies on night shift work and breast cancer risk collectively show an increased breast cancer risk among women. Publication bias is unlikely to have influenced the results.

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1. Introduction

Indirect evidence from observational studies [1-6] suggests an association between melatonin suppression and breast cancer risk, using surrogates for light exposure. Over the past few years, studies of occupational exposure to light at night and the risk of breast cancer

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have been accruing rapidly. The original rationale for studies of flight attendants had been that their occupational exposure to cosmic radiation causes an excess cancer risk. It was reasoned subsequently that the observed increase in breast cancer risk could as well be due to a melatonin deficiency resulting from work-associated exposure to light at night [7]. As a result of a combined effort from members of the European Community, almost ten additional studies have been published since 2000 to explore cancer incidence and mortality in airline cabin crew members [8]. Strikingly, they consistently support the contention that female cabin crew members are at increased risk for breast cancer [9], although the incomplete assessment of possible confounding factors remains an important limitation of these retrospective cohort studies. To date, more than a dozen retrospective and two prospective studies have reported on a relationship between occupational exposure to light at night and breast cancer risk, many of which have been compromised by small case numbers or incomplete adjustment for confounding, particularly the reproductive histories of women [1-6,9].

To overcome some of these limitations, we systematically summarised data from all published studies to evaluate current evidence for an association between occupational light exposure at night and breast cancer risk in women.

2. Patients and methods

2.1. Search strategy and data extraction

We conducted a systematic review of all English and non-English articles using MEDLINE from January 1960 to January 2005. We additionally contacted experts in the field and searched bibliographies and abstracts.

Medical subject heading terms included night work terms: [circadian rhythm or work schedule tolerance or personnel staffing] and [scheduling or night shift or shift work] and flight personnel terms: [flight attendant or flight attendants or cabin crew or cabin crews or flight personnel or airline crew or cabin attendant or cabin attendants or cockpit crew or airline crews or stewardess or stewardesses] with cancer terms: [neoplasms or cancer] and risk terms: [risk or cancer risk or mortality].

Data extraction was conducted by two independent investigators (ESS and SPM), using prespecified eligibility and exclusion criteria.

2.2. Eligible studies

Only observational studies that studied any type of night shift work and breast cancer risk were included (Tables 1 and 2). We did not place any restrictions with regard to place of origin or race of the women. In one instance, two studies based on the same data set were published [2,10]. Only the first study, which reported a standardised incidence ratio (SIR) for breast cancer, as opposed to an odds ratios (OR), was kept in our meta-analysis [2]. As the elevated cancer rates observed in airline cabin crew have previously been attributed to exposure to cosmic radiation, we stratified studies on professional status (*i.e.*, airline cabin crew *versus* any other form of night work).

2.3. Ineligible studies

We excluded animal studies, reviews, and studies that did not provide separate relative risks for breast cancer. Any study that did not separate women from men was also excluded (Figs. 1 and 2). We further did not include cabin crew mortality studies because of the potential insensitivity of mortality studies for relatively nonfatal cancers such as breast cancer. Breast cancer incidence increases do not necessarily result in mortality increases, in part because women with higher socioeconomic status tend to have their cancers diagnosed in earlier stages. Moreover, their stage-adjusted survival rates appear to be higher than those of women from lower social groups [11]. For other types of night work, the only cancer mortality studies published were conducted in male occupational cohorts or did not include breast cancer mortality [12–14].

2.4. Definitions

The outcome of this systematic meta-analysis was histologically confirmed breast cancer. Night shift work was defined as any shift schedule that included overnight work. We included airline cabin crew serving on international or long-distance flights, involving potential circadian rhythm disturbances through exposure to light at night and jet lag.

2.5. Studies identified

We identified 13 studies that met our inclusion criteria. Of these, 7 studied flight attendants (Table 1) and 6 studied other forms of night work (Table 2). Two of the latter were prospective cohort studies [6,15], two were retrospective, population-based cohort studies [3,4], one was a nested case-control study [16], and another was a retrospective case-control study [5], while all seven flight attendant studies were incidence studies with the general population as their referent group. All flight attendant studies were age-adjusted only, but stratified on various, mostly employment related, variables, whereas the studies of other occupational light exposure were adjusted for a varying number of confounding fac-

Table 1			
Study characteristics	of flight	attendant	studies

Study	Country or cohort and time period under observation	Number of breast cancer cases	Covariates that were considered as confounding variables	Standardised incidence rate (SIR)	Standard error (SE)	95% CI
Haldorsen <i>et al.</i> [20]	Retrospective cohort study; 3105 Norwegian airline cabin attendants; those with licenses issued 1950–1994; follow-up from 1953 to 1996	38	Age, calendar period, number of children, age at first birth, length of employment, and length of employment before 26 years old	SIR 1.1	0.18	0.8–1.5
Reynolds <i>et al.</i> [17]	44021 members of the Association of Flight Attendants in California; 1988–1995	60	Age, international <i>versus</i> domestic route, length of service, age at entry	SIR 1.42	0.18	1.09–1.83
Rafnsson <i>et al.</i> [2]	Retrospective cohort study; Iceland; 1532 cabin attendants, from Icelandic Cabin Crew Association and two airline companies; 1955–1997	26	Age, years of employment, hired before or in/after 1971	SIR 1.50	0.29	1.00-2.10
Pukkala <i>et al.</i> [1]	Finland; 1577 female cabin attendants who worked for Finnish airline companies; from files of Finnair Flight Company; follow up from date of recruitment as cabin crew worker or January 1967—whichever was later—and ended at emigration, death, or December 1992	20	Age, calendar period, length of employment	SIR 1.87	0.42	1.15–2.23
Linnersjö [21]	2324 women from Swedish Scandinavian Airline System employed from 1957 to 1994; follow-up from 1961 to 1996	33	Age, calendar period, high altitude, long distance flight hours	SIR 1.30	0.23	0.85–1.74
Lynge [28]	915 female airline cabin attendants in Denmark, followed from 1970 to 1996	14	Age	SIR 1.61	0.27	0.90–2.70
Wartenberg <i>et al.</i> [18]	Survey of 287 retired flight attendants from one US airline; retrospective cohort study	7	Age	SIR 2.00	0.39	1.00-4.30

tors (see Table 1). All eligible studies included Caucasian women; only two studies [17,18] also included women of other ethnicities. The majority of women studied were postmenopausal.

2.6. Data extraction

Data extraction was done by two reviewers (SPM and ESS) using a standardised form. Relative risk (RR) was used as a measure of the relationship between night work and breast cancer risk. For two case-control studies, the odds ratio (OR) was used as a surrogate measure for the corresponding relative risk. In other studies where the comparison group was the general population, standardised incidence ratios (SIR) were used.

2.7. Statistical approach

We performed separate and combined meta-analyses for female airline cabin crew and female night shift workers, using the statistical software STATA [19]. We extracted rate ratios and calculated standard errors. All eligible studies showed a 95% confidence interval (95% CI). Standard errors were derived from confidence limits, applying the formula $SE = \log$ (upper limit of 95% CI/lower limit of 95% CI)/(1.96 * 2). If standardised incidence ratios (SIR) were provided, we applied the formula $SE = \sqrt{O/E^2}$ to derive the standard error [1,17,20,21]. Under the assumption that the person time of the unexposed group is vastly larger than that of the exposed, we made no distinction between standardised morbidity ratios and incidence rate ratios [22] and combined them in our pooled analyses. We used duplicate extraction and checks for errors to ensure accuracy. Based on the standard error, we estimated the weight of each study and pooled risk ratios in our analysis using both fixed-effects and random effects-models for both airline cabin crew and other occupations with night work [23]. Random-effects models tend to produce more conservative estimates. However, the pooled estimates did not differ greatly between random- and fixed-effects models in our analyses.

Table 2	
Study characteristics of night shift wor	k studies

Study	Country or cohort and time period under observation	Source of information for exposure (<i>i.e.</i> , light- at-night exposure)	Definition of light exposure	Profession	Covariates that were considered as confounding variables	OR or RR (extreme group versus referent)	Standard error (SE)	95% CI
Schernhammer et al. [6]	USA, Nurses' Health Study, prospective cohort study; 1988–1998	Self-reported life time years on rotating night shifts, one-timed assessment in 1988	Rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Registered nurses	Age, age at menarche, parity, age at first birth, weight change, BMI, family history of breast cancer, benign breast disease, oral contraceptive use, age at menopause, alcohol consumption, use of postmenopausal hormones, menopausal status, height	1.36 (30+ years of night work <i>versus</i> no night work)	0.14	1.04–1.78
Davis et al. [5]	USA, Case-control study; 1993–1995	An in-person interview was conducted to obtain information on sleeping habits and light exposure and lifetime occupational history	At least one graveyard shift per week (1 shift = 8 h) in 10 years before diagnosis. Graveyard shift work was defined as "beginning work after 7:00 pm and leaving work before 9:00 am"	Not specified	Parity, family history of breast caner (mother or sister), oral contraceptive use (ever), and recent (<5 years) discontinued use of hormone replacement therapy	2.3 (5.7+ h per week of graveyard shift <i>versus</i> no graveyard shift)	0.43	1.0–5.3
Hansen [4]	Denmark, retrospective cohort study; 1964–1999	Individual employment histories were obtained from files of national pension fund	"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."	Various (Hospitals, furniture manufacture, cleaning services, etc.)	Age, social class, age at birth of first child, age at birth of last child, number of children	1.5 (all night work combined in trades with predominantly night work <i>versus</i> women in trades with less than 40% night work)	0.06	1.3–1.7

Tynes et al. [3]	Norway, Telecom cohort of 2619 female radio and telegraph operators certified between 1920 and 1980; follow-up from 1961 to 1991	Collected detailed job histories from Norwegian seamen registry	"Work at night with exposure to artificial light."	Radio and telegraph operators	Age, duration of employment, parity, and age at first birth	1.5	0.15	1.1–2.0
Schernhammer et al. [15]	USA, Nurses Health Study II, prospective cohort study; 1989–2001	Self-reported life time years on rotating night shifts, one-timed assessment in 1989; biannual update	Rotating night shifts were defined as "at least 3 nights per month, in addition to evenings and afternoons in that month"	Registered nurses	Age, age at menarche, parity, age at first birth, BMI, family history of breast cancer, benign breast disease, alcohol consumption, oral contraceptive use, smoking status, menopausal status, age at menopause, physical activity, postmenopausal hormone use	1.79 (20+ years of night work <i>versus</i> no night work)	0.21	1.06–3.01
Lie <i>et al.</i> [16]	Norway, nested case-control study (537 cases and 1:4 matched controls); 1960–1982	Registered nurses: Norwegian Board of Health's registry, censuses, cancer registry	Reconstruction of total work history based on nurse registry and census information; nurses employed at infirmaries were assumed to do night work	Nurses	Total employment time as a nurse and parity; matched by birth year	2.21	0.18	1.10-4.45



Fig. 1. Flow diagram: flight attendants and breast cancer risk.



Fig. 2. Flow diagram: night shift workers and breast cancer risk.

2.8. Evaluation for bias

As the small numbers of studies limits the power of the test for publication bias, we chose to use two different tests to evaluate the possibility of publication bias among the studies. First, we conducted the Begg and Mazumdar adjusted rank correlation test for publication bias [24] and generated a Begg plot. Second, we performed the regression asymmetry test of Egger [25] and generated an Egger plot. Significant test statistics and asymmetry in the plot, especially an empty lower right quadrant (where one would expect to find studies with small effects and high variances), suggest bias. The shape of a funnel plot is largely determined by the arbitrary choice of axes [26]. However, the standard error is likely to be the best choice for the vertical axis [27], and we therefore chose the standard error as the measure of study size and the ratio measures for treatment effects.

3. Results

3.1. Studies included

We identified 13 relative risk estimates for breast cancer from studies that met the inclusion criteria, seven for female airline cabin crew and six for female night shift workers. The characteristics of these studies are presented in Tables 1 and 2.

3.2. Description of studies

Previous studies consistently demonstrated an elevated risk of breast cancer with engagement in any form of night work. The two prospective cohort studies to date of night shift work and breast cancer risk utilized data from the Nurses' Health Study cohorts (NHS and NHSII) [6,15]. In the NHS, Schernhammer and colleagues followed a total of 78,562 US nurses over 10 years (1988–1998): of these women, 2441 incident breast cancer cases were documented during that time. Women who worked at least three nights per month, in addition to evenings and days in that month, were defined as engaging in night work. The relative risk (RR) associated with extended periods (30 or more years) of rotating night work was 1.36 (95% CI, 1.04-1.78), after controlling for known breast-cancer risk factors. The risk increased with increasing numbers of years in shift work (test for trend, P = 0.02). Similarly, in 115,022 predominantly premenopausal women in the NHSII, Schernhammer found an elevated breast cancer risk of 1.79 (95%) CI, 1.06–3.01) among women who worked 20 or more years of rotating night shift work, with 1352 incident breast cancer cases accruing over 12 years of followup (1989-2001).

Two retrospective, population-based cohort studies also found an elevated risk of breast cancer among night shift workers [3,4]. Tynes et al. [3] conducted a study of 2916 female Norwegian radio and telegraph operators certified between 1920 and 1980. Over 30 years of follow-up (1961-1991), they documented 50 incident breast cancer cases. Night work was defined as "work at night with exposure to artificial light" [3]. The relative risk (RR) of breast cancer was 1.5 (95% CI, 1.1–2.0), after controlling for duration of employment. Hansen [4] studied a similar cohort of 7035 women with breast cancer. Their employment histories, covering the period of 1964–1999, were reconstructed, and night work was defined as having worked for at least half a year at a job in which "at least 60% of the female responders had nighttime schedules". The relative risk of breast cancer was 1.5 (95% CI, 1.3–1.7) when all night work from trades that entailed predominantly night work (*i.e.*, $\geq 40\%$ night work) was compared to women in trades with less than 40% night work, after controlling for age, social class, age at birth of first child, age at birth of last child, and number of children. Finally, in a case-control study of 813 women with breast cancer and their 793 matched controls, in-person interviews were conducted from 1992 to 1995 to collect information about their sleeping habits and light exposure during the 10 years before diagnosis and lifetime occupational history [5]. Davis et al. defined night work as at least one graveyard shift per week (1 shift = 8 h) in the 10 years before diagnosis. Graveyard shift work was described as "beginning work after 7:00 pm and leaving work before 9:00 am". The authors observed a relative risk of breast cancer of 2.3 (95% CI, 1.0–5.3) for 5.7+ h per week of graveyard shift versus no graveyard shift, after controlling for parity, family history of breast cancer, oral contraceptive use, as well as recent discontinued use of hormone replacement therapy. A recent retrospective cohort study [16] based on a registry of all Norwegian nurses found an association between longer duration of night work and breast cancer risk similar to that reported in the Nurses' Health Study cohorts (RR associated with 30+ years of night work, 2.21; 95% CI, 1.10-4.45).

Observational studies of cabin crew, with only one exception [20], uniformly indicate a higher breast cancer risk. All seven flight attendant studies are incidence studies with the general population as their referent group [1,2,17,18,20,21,28]. The original rationale for these studies had been that the occupational exposure to cosmic radiation caused an anticipated excess cancer risk. It was reasoned subsequently that the observed increase in breast cancer risk could as well be due to a melatonin deficiency resulting from work associated light exposure at night [7]. In the largest of these studies, Reynolds studied a group of 44,021 female members of the Association of Flight Attendants in California. Of those, 129 cases of breast cancer accrued between 1988 and 1995 [17], and the SIR for breast cancer across all ethnicities was 1.42 (95% CI, 1.09-1.83). Haldorsen [20] evaluated personnel files of 3144 female flight attendants in their study and observed 38 cases of breast cancer during 13 years of followup (1953–1966). The standard incidence ratio (SIR) associated with extended periods of employment (15 or more years) was 0.9 (95% CI, 0.3-2.2), and 1.1 (95% CI, 0.8–1.5) for all women combined. These risks remained largely unchanged after controlling for known breast-cancer risk factors and employment history. However, despite their overall null finding, the authors reported a protective effect of 'not flying' among women aged 26 or younger when compared to three years or more of flying activity before age 26 (SIR, 0.4; 95% CI, 0.1-1.9), which is consistent with all other studies. In 2324 women employed at the Swedish Scandinavian Airline System (SAS), Linnersjö [21] observed 33 cases of breast cancer between 1961

and 1996 and an SIR of breast cancer of 3.27 (95%) CI, 0.44–19.7) among flight attendants, compared to the general population. Two other, similar studies, showed comparable results: Pukkala [1] studied a cohort of 1577 female flight attendants who had worked for Finnish airline companies. During 26 years of follow-up (1967-1992), 20 cases of breast cancer were observed, and the reported SIR was 1.87 (95% CI, 1.15–2.23). Similarly, Rafnsson [2] reported an SIR of 1.5 (95% CI, 1.0-2.1) among 1532 female flight attendants from the Icelandic Cabin Crew Association with 15 or more years of employment, of whom 26 women were diagnosed with breast cancer between 1955 and 1997. Lynge [28] studied a cohort of 915 women registered as flight attendants in Denmark in 1970. After 17 years of follow-up, they reported an SIR of 1.61 (95%) CI, 0.90-2.70) for breast cancer among their female flight attendants. Wartenberg [18] also reported an increased breast cancer incidence in their cohort of retired flight attendants from a US airline (SIR, 2.00; 95% CI, 1.00-4.30).

3.3. Meta-analysis

In fixed effects models, we found a moderately and significantly elevated breast cancer risk among both female airline cabin crew (SIR, 1.44; 95% CI, 1.26–1.65) and among female night workers (RR, 1.51; 95% CI, 1.36–1.68). Overall, the combined estimate for all 13 studies was 1.48 (95% CI, 1.36–1.61; Fig. 3).

As the results of the test for heterogeneity were not significant (P = 0.37 and 0.68, respectively, and 0.62 overall), we based our analyses on fixed-effects models. However, to further explore potential sources of heterogeneity, we examined the role of length of follow-up, year of publication, race, menopausal status, whether data were collected prospectively or retrospectively, and whether adjustment for confounding was complete or not. There was no significant interaction between publication year (P = 0.98), race (P = 0.15), menostatus (P = 0.37), length of follow-up pausal (P = 0.10), and data collection (P = 0.55) and breast cancer rates in meta-regression. Only adjustment for confounding (P = 0.09) was borderline significantly related to breast cancer rates. The negative association in the model adjusting for confounding ($\beta = -0.18$) suggests that the more complete breast cancer risk factors were controlled for in analyses, the more attenuated was a woman's breast cancer risk. There was little evidence that any of the tested variables was a source of heterogeneity in these studies, individually explaining no more than 2% of any variation between the studies. We further conducted a cumulative meta-analysis to derive cumulative pooled estimates, which showed a stable accumulation of evidence for an increased breast cancer risk in the range of 50% after 2001.



Fig. 3. Meta-analysis of all female night workers combined and breast cancer risk in 13 studies. (The dashed vertical line represents the combined estimate, and the diamond-shaped box represents the confidence interval from the random-effects model. The estimates are plotted with boxes; the area of each box is inversely proportional to the estimated effect's variance in the study, hence giving more visual prominence to studies where the effect is more precisely estimated.)

3.4. Evaluation for publication bias

The Egger test for publication bias, regressing breast cancer rates with the inverse of the study variance, showed no evidence for bias in the combined data from studies (intercept estimate 0.70, P = 0.20), and the funnel plots reflected very little asymmetry. Moreover, Begg and Mazumdar's *P*-value of 0.07 was not strongly suggestive of publication bias.

4. Conclusion

This meta-analysis included 13 observational studies that examined breast cancer risk among female shift workers and cabin crew. In pooled results, we found a statistically significant 48% increase in the risk of breast cancer among shift workers. Separate analyses of both shift workers excluding flight attendants and flight attendants yielded virtually identical results.

Exposure to artificial light at night, when the production of melatonin is at its physiological height, sharply reduces levels of melatonin and has been hypothesised to elevate cancer risk [29]. Stevens and Davis [30] proposed that the decreased melatonin production due to exposure to light at night leads to a rise in the levels of reproductive hormones such as oestrogens, thereby inducing hormone sensitive tumours in the breast. Experimental studies support a link between melatonin and tumour suppression, with numerous reports showing that melatonin is oncostatic in a variety of tumour cells. *In vitro* studies indicate that both pharmacological and physiologic doses of melatonin reduce the growth of malignant cells of the breast [31–35] and other tumour sites [36-40]. It was further demonstrated in rodent models that pinealectomy boosts tumour growth [41] whereas exogenous melatonin administration exerts anti-initiating and oncostatic activity [42-46] in chemically induced cancers. Melatonin's oncostatic activities span a wide range of immunomodulating actions. The most prominent mechanisms that have been proposed to explain the oncostatic action of melatonin include the hormone's antimitotic [47] and limited antioxidant activity [47,48] as well as potential modulation of cellcycle length through control of the p53-p21 pathway [34]. Furthermore, circadian stage dependent biochemical interactions between melatonin and fatty acid metabolism were defined by Blask [49] and have been associated with cancer growth inhibition in rodent models. Finally, to date, several clinical trials confirm the potential of melatonin, either alone or in combination with standard therapy regimens, to generate a favorable response in the treatment of human cancers [50].

Consistent with these mechanisms and regardless of study type, previous research has consistently shown an elevated risk of breast cancer with engagement in night work. Although mortality studies are not included in our report, a large European mortality study [51] based on airline cabin crew data from eight different countries found a modestly elevated breast cancer mortality (SMR, 1.11, 95% CI, 0.82–1.46), with an overall reduced morality from cancer in their female airline cabin crew. Considering the relative insensitivity of mortality studies for nonfatal cancers such as breast cancer and better survival of cancer patients from higher social position [52], this finding may be in line with the summary relative risk from our meta-analysis.

Incomplete adjustment for confounding remains a limitation of many of the studies included in this meta-analysis. However, the aggregate breast cancer risk in airline cabin crew, which was based on studies that were age-adjusted only, was virtually identical to that of other night workers, whose aggregate risk estimate was based on studies that, by and large, have been adjusted for breast cancer risk factors. Information on overhaul flights versus inland flights was not available in many of the flight attendant studies. It is more likely that long distance flights rather than inland flights induce circadian disruption. Thus, the lack of this information may potentially have lead to a risk underestimation in airline personnel. Moreover, the assessment of employment time was oftentimes based on crude estimates and is likely to be misclassified, but such misclassification would only have attenuated the relative risk estimates.

In summary, this meta-analysis suggests that shift work, including work as a flight attendant, increases the risk of breast cancer by 48%. The fact that risks for both flight attendants and other night work occupations were essentially identical provides an argument against previous theories suggesting that the increased incidence of breast cancer in flight attendants is due to effects of increased radiation or electromagnetic exposure. Rather, the observed increased risk of breast cancer may be associated with engagement in night work and a related decrease in melatonin production.

Conflict of interest statement

None declared.

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