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Nightshift work and risk of breast cancer and other cancers—a critical review of the epidemiologic evidence

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Key terms: breast cancer; cancer; chronobiology disorder; circadian rhythm; epidemiologic evidence; nightshift work; occupational exposure; occupational health; review; risk; shift work

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Review

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Nightshift work and risk of breast cancer and other cancers—a critical review of the epidemiologic evidence

by Henrik A Kolstad, MD [1]

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Objectives This systematic review concerns the role of nightshift work in the risk of breast cancer or other cancers.

Methods Studies that specifically included information on nightshift or shift work and reported cancer occurrence were focused upon. A systematic search of Medline and the Science Citation Index was conducted until May 2007. The quality of each paper was discussed with respect to design, exposure and outcome information, bias, confounding, and exposure–response assessment.

Results Thirteen relevant reports were found, and eight reported the relative risk for breast cancer, three for prostate cancer, three for colon cancer, and four for all cancers. Most of the studies had crude information about nightshift work, four register-linked studies had no individual exposure information but relied on exposure probabilities assessed on a group level, and no studies analyzed cancer risk according to the cumulative number of night shifts (however, most of the studies did so according to the number of years of nightshift work). Confounding did not seem to be of major concern. The presentation of the results was not always complete, and it would have been appreciated if the reasons for leaving some findings out had been reported. There were indications of a long-term effect of nightshift work (more than 20–30 years), but the number of positive studies was small. In addition, they were all conducted among nurses, and the risk estimates were only moderately increased. This situation makes the results sensitive to bias, chance, and confounding.

Conclusions There is limited evidence for a causal association between nightshift work and breast cancer, while there is insufficient evidence for prostate cancer, colon cancer, and overall cancer.

Key terms chronobiology disorder; circadian rhythm; occupational exposure; occupational health; shift work.

In 1987, it was hypothesized that the rising risk of breast cancer seen in industrialized societies was, at least partly, due to the increased use of electric lighting at night (1). It was suggested that light at night could suppress melatonin output and increase estrogen levels and thereby increase the risk of breast cancer. The idea was based on experiments with rodents, which showed that constant light affected mammary tumorigenesis, and epidemiologic results that breast cancer risk was highest in the most-industrialized societies. The melatonin hypothesis stimulated various lines of research, from laboratory studies using animal models to epidemiologic studies of humans exposed to light at night and nightshift work. Recently, the hypothesis has evolved from merely a question of suppression of melatonin output to a question of disruption of the circadian rhythm, interaction with clock genes, and light exposures in early life (2).

Megdal et al (3) reviewed the epidemiologic evidence of nightshift work and breast cancer in 2005. My review is focused on prostate, colon, and all cancers, in addition to breast cancer. It includes six studies not included in the earlier review (4–9), and it leaves out seven studies of flight attendants that provided no information about nightshift work.

Altogether 429 900 European women were diagnosed with breast cancer in 2006, and breast cancer has become the most common form of cancer in Europe (13.5% of all cancer cases) (10). Fifty percent of all breast cancer cases can be attributed to known risk factors (11), primarily prolonged exposure to endogenous and exogenous female sex hormones (12–15), but also alcohol (16), adiposity, and excessive weight gain (17).

About 20% of employees or self-employed workers in the countries in the European Union (EU) work at least one night a month (at least 2 hours between 2200

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and 0500) (18). Ten percent work 1–5 nights, and 10% work more than 5 nights per month. Furthermore, 0.4% work permanent night shifts (19). Night work is the most prevalent (>30%) in agriculture, hotels, restaurants, transport, communication, and health (18).

Exposures of nightshift work

Light

In offices and hospitals, the illuminance at the cornea is about 100–300 lux during night and daytime work compared with 10 000 lux outdoors during the day and 0.1–5 lux when asleep during the night and day (20). A threshold level of 30 lux of white light has been suggested for melatonin suppression (20).

Behavioral factors

A previous review reported that 9 out of 11 studies showed 1.07–1.48 times more smokers among shift workers than among day workers, while two studies showed reduced prevalence ratios (0.56 and 0.96) (21). That review documented no strong indications that alcohol consumption or exercise differ between shift workers and day workers. Only few differences were observed with respect to nutritional intake. However, the frequency and timing of meals may change during shift work, and there were some indications that shift workers are heavier than day workers (2 of 10 studies; 8 showed no difference).

The distribution of behavioral factors among nightshift and day workers was reported in five of the studies included in this review (6, 7, 22–25). Table 1 presents an overview of this information and shows that nightshift workers more often smoke (an average of about 20–30% more smokers), have a higher body mass index (BMI), and less often use hormone replacement therapy than day workers. Nightshift workers also seem to have early menarche more often, but no consistent patterns were apparent for other reproductive factors across the five studies. It should, however, be noted that a 3–6 times higher alcohol consumption was reported for nightshift workers than for day workers in one study (25).

Table 1. Characteristics of nightshift workers relative to day workers. Results of five epidemiologic studies in 2001–2007. (F = female, M = male, ↑ = characteristic more prevalent or more pronounced among nightshift workers than among daytime workers, ↓ = characteristic less prevalent or less pronounced among nightshift workers than among daytime workers, 0 = no substantial difference between nightshift and daytime workers, BMI = body mass index, HRT = hormone replacement therapy)

Characteristic	Prevalence or magnitude of characteristic among nightshift workers relative to daytime workers by study [a]				
	Schernhammer et al, 2001 (22); Schernhammer et al, 2003 (23)	O'Leary et al, 2006 (6)	Schernhammer et al, 2006 (24)	Kubo et al, 2006 (7)	Hansen, 2001 (25)
Gender	F	F	F	M	F
Age	↑	↓	↑	..	..
Early menarche	↑ (Age at menarche <12 years: 26.3% versus 21.8%)	..	↑ (Age at menarche <14 years: 86% versus 83%)	..	..
Nulliparous	0	↓	..	..	..
Postmenopausal	↑	↓	↑	..	..
Young at first birth	↓	..	↑	..	..
Body mass index	↑ (BMI >25 kg/m^2: 42.7% versus 40.1%)	..	↑ (BMI, kg/m^2: 28.9 versus 25.4)	↑ (BMI >23.9 kg/m^2: 34.4% versus 30.8%)	..
Family history	0	↓	0	↑	..
Benign breast disease	↓	↑	↑	..	..
Oral contraceptive	↓	↑	0	..	..
Hormone replacement therapy	↓ (Current HRT ≥ years: 9.1% versus 10.9%)	↓ (Ever HRT: 24.0% versus 34.4%)	..	..	..
Physical activity	..	..	..	↓	..
Alcohol	↓	↑	↓	0	↑
Smoking	↑ (Current or former smoker: 24.6% versus 17.4%)	↑ (Current smokers: 14% versus 10%)	↑ (Current or former smoker: 78.2% versus 76.5%)		
Socioeconomic status	↓	0	..	..	..
Indoor work	..	..	..	↑	..

[a] If consistent across the studies, detailed results are presented in parentheses.

Sleep deprivation and stress

Nightshift workers often complain about insufficient sleep because the quality of daytime sleep may be worse than nighttime sleep (20, 26). Activation of the hypothalamic-pituitary-adrenal (HPA) axis has been suggested as a major mediator of illness and disease (eg, cardiovascular disease) among shift workers (27), and shift work is related to lower job control, but no difference in work demands (28).

Melatonin in nightshift workers

A large field study of nurses recently showed a lower concentration of urinary 6-sulfatoxy melatonin (the major metabolite in urine) in mixed shift workers during their nightshifts than during their days off (intra-individual comparisons) and also a lower concentration than that of fixed dayshift workers (interindividual comparisons) (29). Urinary 6-sulfatoxy melatonin levels were specified for 3-hour intervals during 24-hour periods. Fixed nightshift workers showed somewhat lower concentrations, of borderline statistical significance, than mixed nightshift workers during nightshift workdays. Twenty-four-hour 6-sulfatoxy melatonin output was not reported, but it showed no significant association with nightshift work (personal communication, Åse Marie Hansen). Borugian et al (30) found lower 24-hour melatonin levels among rotating shift workers during night shifts but higher levels during day shifts or days off than for day workers. Shernhammer et al (31) showed lowered 6-sulfatoxy melatonin levels in the morning urine of 14 nurses that worked at least one night shift during the previous 2 weeks than for nurses working no night shifts during this period.

Methods

Three methods were used in combination to identify the epidemiologic literature relevant to nightshift work and cancer risk. First, a computerized search was conducted in PubMed in May 2007. Search terms included night work, night shift, or shift work (text words) or circadian rhythm, work schedule tolerance, circadian disruption and chronobiology disorders (MeSH terms or subheadings) and cancer (text term) or neoplasms and risk, rate, odds ratio, incidence, or mortality (MeSH terms). Then references were extracted from the bibliographies of the articles identified. All of the abstracts were reviewed, and the final set of studies was decided upon. I included original epidemiologic studies that specifically had information on night or shift work and the risk of cancer. No animal studies were included. Finally, I conducted a search in Science Citation Index that was based on three core publications (22, 25, 32).

Altogether 426 articles were identified. After the abstracts were reviewed, 61 articles were selected for a detailed evaluation. Of these, 12 were original epidemiologic studies of night or shift workers and cancer risk

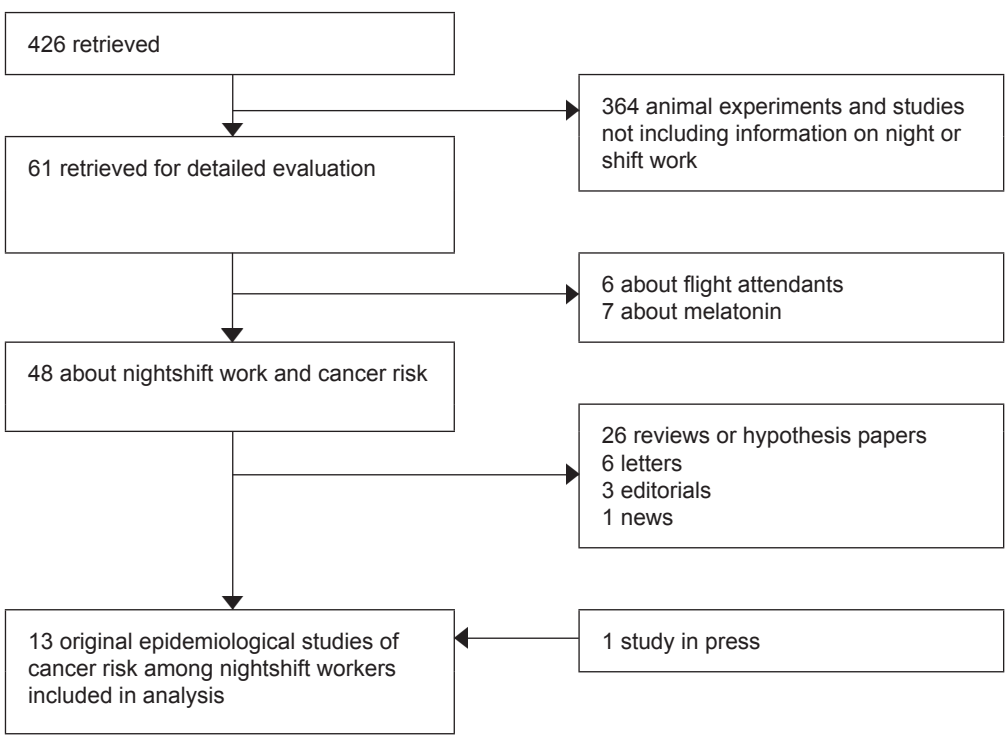

Figure 1. Flowchart—nightshift work and risk of cancer.

and thus met the inclusion criteria (4–8, 22–25, 32–34) (figure 1). I also identified 26 reviews or hypothesis papers (2, 3, 20, 35–57), 6 letters (58–63), 3 editorials (64–66), and 1 news report (67) in addition to 6 papers focusing on flight attendants (68–73) and 7 focusing specifically on melatonin (74–79). Finally, I included the study by Schwartzbaum et al that was accepted for publication but not yet published in the *Scandinavian Journal of Work Environment & Health* (9).

The 13 selected studies included 8 studies on breast cancer (6, 9, 22, 24, 25, 32–34), 3 studies on prostate cancer (7–9), 3 studies on colon cancer (9, 23, 33), and 4 studies on all cancer (4, 5, 9, 33). Tynes et al (33) reported the risk of breast cancer, colon cancer, and all cancer, and Schwartzbaum et al (9) reported the risk of breast cancer, prostate cancer, colon cancer, and all cancer. Tynes et al (33) and Schwartzbaum et al (9) reported on other major cancer sites as well, but I only reviewed sites studied in at least three studies. The 2001 study about breast cancer and the 2003 study about colon cancer by Schernhammer et al were based on the same study population (22, 23), which did not overlap with the 2006 study about breast cancer (24). Table 2 presents the main characteristics of the 13 studies, and table 3 presents the principal results, cancer site by cancer site.

Epidemiologic studies of pilots, flight attendants, physicians, radiologists, military and police employees, fire fighters, or police or law enforcement personnel that have been included in previous reviews were not included (45, 52), since these studies did not specifically include any information about nightshift work for the study participants. The former review authored by Megdal and her colleagues (3) focused on cancer risk among aircrew, and I therefore included studies of airline flight attendants and pilots, in addition to other relevant toxicologic and epidemiologic data in the section with contributory evidence. That part of the review is not comprehensive or systematic; instead the intention was to include a balanced set of the most relevant studies.

Finally, the degree of evidence for causal associations between nightshift work and each of the reviewed cancer sites was rated according to the criteria of the Scientific Committee of the Danish Society of Occupational

Table 2. Main characteristics of 13 epidemiologic studies of nightshift work and risk of cancer, 1972–2007. (ICD-O = International Classification of Diseases for Oncology; ICD-7 = International Classification of Diseases, 7th revision; BMI = body mass index)

Study	Cancer sites included in review	Design, study population, study period and number of participants (participation rate)	Source of exposure information	Measure of exposure (prevalence in study base) and exposure period	Source of outcome information and latency or induction period	Controlled covariates	Exposure–response assessment
Tynes et al, 1996 (33); Norway	Breast, colon, all cancer	Nested case–control register-linked study within cohort of telegraph operators, 1961–1991; 50 breast cancer cases, 259 age-matched controls, 140 all cancers (98%)	Journalist- and researcher-classified ships according to extent of shift work	Four categories (0–3) reflecting presence in radio room during day and night (83–90%); total work history since certification	National cancer register; separate analyses for exposures prior to 30 years of age and risk before or after 50 years of age	Duration of employment and age at first birth (3 levels) for women born ≥1935	Duration (years) and shiftwork category × duration; test for trend of continuous term
Davis et al, 2001 (32); United States	Breast	Population-based case–control study, 1992–1995; 767 cases (78%) and 743 controls (75%)	Questionnaire at diagnosis or on reference date	Graveyard shift: beginning after 1900 and ending before 0900 (3–5%); 10 years prior to diagnosis or reference date; information on graveyard shifts during total work history was obtained but no risk estimates reported	Regional cancer register; no analyses by latency	Age, parity, family history, oral contraceptives, and hormone-replacement therapy	Hours/week and duration (years); test for trend of continuous term
Schernhammer et al, 2001 (22); United States	Breast	Prospective cohort of nurses, 1988–1998; 78 562; 2441 cases (82%)	Questionnaire at baseline (1988)	Rotating night shifts; at least 3 nights/month, in addition to days or evenings in that month (60%); total work history prior to baseline	Self-reports confirmed by medical records or national death index; pathology reports for 93%; no analyses by latency	Age, age at menarche, parity, age at first birth, weight change, BMI, family history, benign breast disease, oral contraceptives, alcohol, calendar year, age at menopause, hormone replacement therapy, menopausal status and height	Duration on rotating night shifts (years): never, 1–14,15–29, ≥30; test for trend of continuous term
Hansen, 2001 (25); Denmark	Breast	Population-based register-linked nested case–control study, study period not reported; 6281 cases (93%) and individually matched 6024 controls (participation rate not reported)	Records of national pension fund	Job exposure matrix classified 4 trades with at least 60% employees working predominantly at night (5%); total work history since 1964	National cancer register; 5-year latency period	Number of children, age at birth of first and last child, current job title	No exposure–response assessment; >6 years of employment reported separately

(continued)

Table 2. Continued.

Study	Cancer sites included in review	Design, study population, study period and number of participants (participation rate)	Source of exposure information	Measure of exposure (prevalence in study base) and exposure period	Source of outcome information and latency or induction period	Controlled covariates	Exposure–response assessment
Lie et al, 2005 (34); Norway	Breast	Register-linked case–control study of nurses, 1960–1982; 537 cases, 2143 controls matched by year of birth (participation rate not reported)	National register of nurses and national censuses	Work at infirmaries, except managerial, teaching, physiotherapy work or work in outpatient departments (90%); total work history	National cancer register; 20-year latency period	Age at birth of first child, number of children, and total employment time	Duration (years) of work in infirmaries
Schernhammer et al, 2006 (24); United States	Breast	Prospective cohort of nurses, 1989–2001; 115 022; 1352 cases (99.5%)	Questionnaire at baseline (1989) and in 1991, 1993, 1997 and 2001	Rotating night shifts, at least 3 nights/month, in addition to days or evenings in that month (68%); total work history prior to diagnosis; information on permanent night shifts were obtained but not reported	Self-reports confirmed by medical records or national death index; pathology reports for 98%; no analyses by latency	Age, age at menarche, menopausal status, age at menopause, age at first birth and parity, BMI, alcohol consumption, oral contraceptives, hormone-replacement therapy, smoking, benign breast disease, family history, and physical activity	Duration (years) of rotating night shifts: never, 1–9, 10–19, ≥20; test for trend of continuous term
O'Leary et al, 2006 (6); United States	Breast	Population-based case–control study, 1996–1997; 487 cases (?%) and 509 controls (?%)	Interview at diagnosis or on reference date	Overnight shifts; starting after 1900 and continuing to the following morning (10%); 15 years prior to diagnosis or reference date	Weekly hospital contacts; no analyses by latency	Age, parity, family history, education, benign breast disease	Duration (years) of overnight shift work
Schwartzbaum et al, 2007 (9); Sweden	Breast, prostate, colon, all cancer	Population-based register-linked cohort study, 1971–1989, of gainfully employed (≥20 hours/week) in 1960 and 1970; 69 759 men and 3057 women, 6792 cancer cases (participation rate not reported)	Population censuses in 1960 and 1970	Job title and industry combinations classified by job-exposure matrix with at least 40% working rotating shifts (3 or more shifts per day) or working any hour 0100–0400 at least once a week (3% of men and 0.3% of women); 1960–1970	National cancer register; no analyses by latency	Age, socioeconomic status, occupational position, county of residence, marital status, urbanization	Shift work in 1960 and 1970 as proxy for duration of shift work (>10 years)
Kubo et al, 2006 (7); Japan	Prostate	Prospective population-based cohort study, 1988–1997; 14 052; 31 cases (83%)	Questionnaire at baseline	The longest held work schedule; fixed night work (7%) and alternate night and day work (13%)	Regional cancer registers	Age, study area, family history, BMI, smoking, alcohol, job type, physical activity, stress, education, marriage status	No exposure–response assessment
Conlon et al, 2007 (8); Canada	Prostate	Population-based case–control study, 1995–1998; 760 cases, 1632 age-matched controls (response rate not reported)	Questionnaire filled out retrospectively	Full-time rotating shifts (44%); total work history; information on part-time rotating shifts and evening or night shifts were obtained but no risk estimates were reported	Cancer registry; four-level latency analysis	Age and family history	Duration (years) of full-time rotating shifts
Schernhammer et al, 2003 (23); United States	Colon	Prospective cohort of nurses, 1988–1998; 78 586; 347 colon cancer cases and 103 rectal cancer cases (82%)	Questionnaire at baseline (1988)	Rotating night shifts; at least 3 nights/month, in addition to days or evenings in that month (60%); total work history prior to baseline	Self-reported cases confirmed by medical records or national death index	Age, smoking, BMI, physical activity, aspirin use, screening endoscopy, diet, alcohol, caloric intake, hormone-replacement therapy, height	Duration (years) of rotating night shifts: never, 1–14, ≥15; test for trend of continuous term
Taylor et al, 1972 (4); United Kingdom	All cancer	Retrospective cohort of industrial workers with >10 years of employment, 1956–1968; 4188; 248 cases (99.75%)	Pay rolls	Three-shift weekly rotating, 3-shift rapid rotating, alternate day and night (99%)	Death certificates	Age and calendar year	No exposure–response assessment
Rafnsson et al, 1990 (5); Iceland	All cancer	Retrospective cohort of workers at fertilizer plant, 1954–1985; 211; 10 cases	Pay rolls	Three shifts; total work history in plant	Mortality data from national bureau of statistics	Age and calendar year	Duration (years)

and Environmental Medicine (appendix 1). The key criterion was the epidemiologic evidence, while studies with experimental animals were considered to add only to the final classification.

Results

Indivdual studies

Breast cancer. *Tynes et al* (33) conducted a register-

Table 3. Nightshift work and relative occurrence (RO) of cancer, overall results, and results by duration of nightshift work—findings of

Study	Overall [a]				Duration of nightshift work [a]						
					Reference			Short duration			
	RO	95% CI	Cases (N)	Exposure definition	RO	Cases (N)	Duration definition	RO	95% CI	Cases (N)	Duration definition
Breast cancer											
Tynes et al, 1996 (33); Norway											
<50 years of age	·	·	–	·	1 [a]	3	0 years	0.9 [a]	0.2–3.7	13	1–3.1 years
≥50 years of age	·	·	–	·	1 [a]	1	0 years	1.9 [a]	0.2–17.9	5	1–3.1 years
Davis et al, 2001 (32); US	1.6 [a]	1.0–2.5	54	Ever nightshift	1 [a]	733	<1 nightshift/week	1.4 [a]	0.6–3.2	15	1–3 years
Schernhammer et al, 2001 (22); US	·	·	–	·	1 [b]	925	Never	1.08 [b]	0.99–1.18	1324	1–14 years
Hansen, 2001 (25); Denmark	1.5 [a]	1.3–1.7	434	≥½ year in selected occup	1 [a]	5847	Daytime work	·	·	–	·
Lie et al, 2005 (34); Norway	·	·	–	·	1 [a]	50	0 years	0.95 [a]	0.67–1.33	362	1–14 years
Schernhammer et al, 2006 (24); US	·	·	–	·	1 [b]	441	Never	0.98 [b]	0.87–1.10	816	1–9 years
O'Leary et al, 2006 (6); US	0.55 [a]	0.32–0.94	26	Ever nightshift	1 [a]	469	<1 nightshift/week	0.74 [a]	0.32–1.68	11	1–8 years
Schwartzbaum et al, 2007 (9); Sweden	0.94 [c]	0.74–1.18	70	≥20 hours/week in selected occup	1 [c]	NR	<30% shift workers in occup	·	·	–	·
Prostate cancer											
Kubo et al, 2006 (7); Japan											
Fixed night shifts	2.3 [b]	0.6–9.2	3	Longest form of work	·	–	·	·	·	–	·
Rotating shifts	3.0 [b]	1.2–7.7	7	Longest form of work	·	–	·	·	·	–	·
Conlon et al, 2007 (8); Canada	1.19 [a]	1.00–1.42	369	Ever ≥1 year nightshift	1 [a]	391	Never	1.44 [a]	1.10–1.87	115	1–6 years
Schwartzbaum et al, 2007 (9); Sweden	1.04 [c]	0.99–1.10	1319	≥20 hours/week in selected occup	1 [c]	NR	<30% shift workers in occup	·	·	–	·
Colon cancer											
Tynes et al, 1996 (33); Norway	1.3 [c]	0.6–2.6	9	Ever radio or telegraph operator	·	–	·	·	·	–	·
Schernhammer et al, 2003 (23); US	·	·	–	·	1 [b]	137	Never	0.93 [b]	0.74–1.17	169	1–14 years
Schwartzbaum et al, 2007 (9)	1.03 [c]	0.94–1.13	449	≥20 hours/week in selected occup	1 [c]	–	<30% shift workers in occup	·	·	–	·
All cancer											
Taylor et al, 1972 (4); UK	1.16 [d, e]	·	219	≥10 years of shift work	·	–	·	·	·	–	·
Rafnsson et al, 1990 (5); Iceland	1.40 [f]	·	14	≥1 year shift work	·	–	·	4.12 [f]	·	4	≤1 year
Tynes et al, 1996 (33); Norway	1.2 [c]	1.0–1.4	–	Ever radio or telegraph operator	·	–	·	·	·	–	·
Schwartzbaum et al, 2007 (9); Sweden	1.02 [c]	1.00–1.05	6524	≥20 hours/week in selected occup	1 [c]	NR	<30% shift workers in occup	·	·	–	·

[a] Odds ratio. [b] Relative risk. [c] Standardized incidence ratio. [d] Standardized mortality ratio (computed from the presented data).

linked case–control study among 2619 women recorded in a national register of certified radio and telegraph operators who had primarily worked in the merchant navy. A total of 50 incident breast cancers [International Classification of Diseases 7th revision (ICD-7) 170] were identified in a national cancer register, and 259 age-matched controls were drawn from within the study population. Histories of employment on ships were obtained from a seamen register, and a shipping journalist and a researcher with detailed knowledge of the merchant navy classified each ship with respect to shift work (4 categories: 0, 1, 2, 3). It was stated that

13 epidemiologic studies, 1972–2007. [US = United States, occup = occupation(s), UK = United Kingdom, NR = not reported]

Duration of nightshift work (continues) [a]												Test for t-trend (P-value)
Medium duration				Long duration I				Long duration II				
RO	95% CI	Cases (N)	Duration definition	RO	95% CI	Cases (N)	Duration definition	RO	95% CI	Cases (N)	Duration definition	
0.8 [a]	0.2–3.6	13	3.2–14.6 years	.	.	–	.	.	.	..	.	0.80
5.9 [a]	0.7–47.7	15	3.2–14.6 years	.	.	–	.	.	.	..	.	0.02
1.6 [a]	0.8–3.2	19	≥3 years	.	.	–	.	.	.	..	.	0.04
1.08 [b]	0.90–1.30	134	15–29 years	1.36 [b]	1.04–1.78	58	≥30 years	.	.	..	.	0.02
1.7 [a]	1.3–1.7	63	>6 years	.	.	–	.	.	.	..	.	..
1.29 [a]	0.82–2.02	101	15–29 years	2.21 [a]	1.10–4.45	24	≥30 years	.	.	..	.	0.01
0.91 [b]	0.72–1.16	80	10–19 years	1.79 [b]	1.06–3.01	15	≥20 years	.	.	..	.	0.65
0.32 [a]	0.12–0.83	6	≥8 years	.	.	–	.	.	.	..	.	..
0.97 [c]	0.67–1.40	28	>10 years	.	.	–	.	.	.	..	.	..
.	.	–	.	.	.	–	.	.	.	..	.	..
.	.	–	.	.	.	–	.	.	.	..	.	..
1.14 [a]	0.86–1.52	87	7–21 years	0.93 [a]	0.70–1.23	81	22–33	1.30 [a]	0.97–1.74	86	≥34 years	0.42
1.02 [c]	0.95–1.10	780	>10 years	.	.	–	.	.	.	..	.	..
.	.	–	.	.	.	–	.	.	.	..	.	..
1.32 [b]	0.93–1.87	41	≥15 years	.	.	–	.	.	.	..	.	0.20
1.02 [c]	0.90–1.15	266	>10 years	.	.	–	.	.	.	..	.	..
.	.	–	.	.	.	–	.	.	.	..	.	..
2.02 [f]	.	2	2–5 years	1.71 [f]	.	5	6–15 years	0.59 [f]	.	3	≥16 years	..
.	.	–	.	.	.	–	.	.	.	..	.	..
1.01 [c]	0.98–1.05	3799	>10 years	.	.	–	.	.	.	..	.	..

[a] P<0.05. [f] Standardized mortality ratio.

this classification reflected frequent presence in the radio room both at night and during the day. The shiftwork variable was multiplied by the number of years employed within each category (this information was however not clearly stated), and this index was used together with the duration of employment in the analyses. The analyses were adjusted for a fertility variable (no children, age <25 years at birth of first child, age ≥25 years at birth of first child), but only for participants born in 1935 or later (this information was available for 6 out of 21 cases >50 years of age; apparently information was complete for participants <50 years of age). Data were

presented separately for women <50 years of age and those ≥50 years of age.

The odds ratio (OR) of breast cancer increased by duration of employment (P-value = 0.02), and, for the operators employed for more than 3.1 years (the highest category), an odds ratio of 5.9 [95% confidence interval (95% CI) 0.7–47.7] was observed when the group was compared with operators never undertaking nightshift work among those aged ≥50 years. Similar findings were found if the odds ratio was analyzed according to the cumulative index.

For the operators who were not yet 50 years of age, there was no excess. Comparable results were found in analyses including only work histories before the age of 30 years.

Davis et al (32) conducted a population-based case–control study of nightshift work and breast cancer. The case patients were women aged 20–74 years, diagnosed with breast cancer [International Classification of Diseases for Oncology (ICD-O) 174.0–174.9] between 1992 and 1995, and identified by the SEER (surveillance, epidemiology, and ends results) cancer surveillance program. Age- and sex-matched controls were identified by random-digit dialing. Altogether 78% of the cases and 75% of the controls agreed to participate. Through individual interviews a lifetime occupational history was obtained that included any job lasting 6 months or longer. For each job, the percentage of time worked during the day, during the evening, and on the graveyard shift was requested. The graveyard shift was defined as "beginning work after 1900 and leaving work before 0900". For the 10 years prior to a diagnosis, the following three variables further characterized the graveyard shift: (i) ever worked the graveyard shift, (ii) hours per week on the graveyard shift, and (iii) number of years of at least one graveyard shift per week.

The adjusted odds ratio for breast cancer for ever working the graveyard shift during the 10 years prior to a diagnosis was 1.6 (95% CI 1.0–2.5). The risk increased by number of hours per week on the graveyard shift (P-value, test for trend 0.03) and by the number of years with at least one graveyard shift per week (P-value, test for trend 0.04) within this 10-year period. These analyses were adjusted for parity, family history of breast cancer, oral contraceptive use, and hormone replacement therapy.

No results were presented for lifetime work history.

Schernhammer et al (22) studied the risk of breast cancer following work on rotating nightshifts among nurses participating in the United States (US) Nurses' Health Study. The study enrolled 121 701 female nurses aged 30–55 years in 1988. After exclusions were made for those with incomplete data or previous cancer, 78 562 nurses comprised the study population that was followed until 1998. The participants in 1988 completed a questionnaire that included questions about nightshift work that was defined as "rotating night shifts with at least three nights per month in addition to days or evenings". The participants reported whether or not they had been diagnosed with breast cancer, and the national death index was searched for additional cases. Altogether a total of 2441 cases of breast cancer were ascertained between 1988 and 1998. Pathology records were identified for 93%.

The risk of breast cancer, adjusted for a comprehensive list of known, potential confounders, increased as the number of years on rotating shifts increased up to 1988 in a comparison with those who never had such work prior to 1988 (P-value for trend 0.02). For those with more than 30 years on rotating shifts, the adjusted relative risk (aRR) was 1.36 (95% CI 1.04–1.78). Comparable results were found for pre- and postmenopausal women. Risk estimates adjusted for age only were almost identical to those obtained in the full models.

Hansen (25) reported breast cancer risk among women employed in the manufacture of beverages, in land transport services, in catering, and in air transport services in a register-linked nested case–control study. Women aged 30–54 years (N=7035) with breast cancer were identified in the national cancer register. Individually matched controls were obtained from a national population register. Employment histories since 1964 were obtained for the cases and controls from a national pension fund. A survey conducted in 1976 showed the highest prevalence of female workers with nighttime schedules (64–71%) in these four trades.

The odds ratio for breast cancer among women ever employed for >6 months in these trades was 1.5 (95% CI 1.3–1.7) when they were compared with women employed in trades with less than 40% female employees working nighttime schedules according to the survey. Trades with 40–60% female nighttime workers were excluded from the analyses. The analyses were adjusted for the number of children, age at birth of first child and age at birth of last child, and current job title. The 1976 survey showed that the average number of alcoholic drinks consumed was substantially higher (3–6 times the median value for all female employees) in the four exposed trades. It was stated that there was a positive trend towards breast cancer risk according to the duration of work at night, but only the results for those employed for >6 years in the exposed trades were presented (OR 1.7, 95% CI 1.3–1.7). Taking account of time since first employment did not influence the risk estimates substantially.

Lie et al (34) studied 537 breast cancer cases and 2143 individually matched controls in a register-linked study within a cohort of 44 853 female nurses registered in a national register of nurses. The register included nurses who had graduated from a nursing school in

Norway between 1914 and 1980 and were alive in 1949 or born later. The cases were identified in the national cancer register (ICD-7 codes). For each case, four controls alive and without breast cancer at the time the cases were diagnosed were randomly drawn from the cohort and individually matched by year of birth.

Work histories were reconstructed from the register of nurses. This register included self-reported information on workplace and, to some extent, ward or department for the period prior to 1968 (the last regular update) and only sporadically thereafter. Additional data were obtained from 1960, 1970, and 1980 censuses if the occupational code was "nursing" or "nursing and other care work" or the industry code was "health work". All work at infirmaries was defined as night work, except for managerial jobs, teaching, and work in physiotherapy or outpatient departments. Information on workplace was incomplete after 1960 because the censuses did not include information on workplace.

The odds ratios were analyzed using a conditional logistic regression adjusted for age at birth of first child, number of children, and total employment time. The adjusted odds ratio for breast cancer increased as the years with night work increased, as defined by the authors, and the risk was increased twofold if night work had lasted ≥30 years as compared with no night work. A test for trend showed a P-value of 0.01. A similar pattern was found if the last 20 years of employment were disregarded.

Schernhammer et al (24) analyzed rotating night shifts and the relative risk of breast cancer in the Nurses' Health Study II that enrolled 115 022 nurses aged 25–42 years in 1989. The population did not overlap that studied by Schernhammer in 2001 (22). The participants filled out questionnaires about night work in 1989, 1991, 1993, and 1997 and retrospectively in 2001 for the time periods 1993–1995 and 1997–1999. Rotating nightshift work was defined as in the previous report (22). Questions were asked about months working rotating nightshifts in six categories (0, 1–4, 5–9, 10–14, 15–19 and ≥20 months) and permanent night shifts for ≥6 months. In the analyses the participants were classified by the lifetime total number of years they had worked rotating night shifts until the date of diagnosis. Other procedures were comparable with the analyses based on the Nurses' Health Study I. Nurses who reported >20 years of rotating nightshift work showed an elevated relative risk (RR) of breast cancer when compared with nurses never working rotating nightshifts (RR 1.79, 95% CI 1.06–3.01) after adjustment for multiple potential confounding factors (but this procedure did not change the results substantially from the age-adjusted RR estimates). There was no increased risk with fewer years of working on rotating nightshifts. No results were presented for permanent nightshift work.

O'Leary et al (6) conducted a population-based case–control study of breast cancer in 1996–1997 in Long Island, New York. They included 467 cases and 509 controls recruited through a multistep procedure, and the participation rates were not easily computable. The cases were newly diagnosed patients with first primary invasive or in situ breast cancer identified by weekly contacts to hospitals, pathology departments, and physicians in the study area (80). Occupational histories were obtained for all of the jobs held for ≥6 months during the 15 years prior to the diagnosis (cases) or reference (controls) date. The frequency (days per week, month, and year), duration, and type of shift work were ascertained for each job, and the participants were specifically asked about overnight shifts defined as "starting as early as 1900 and continuing until the next morning". Among the cases 5.3%, and among the controls 9.8%, had ever worked overnight shifts during the previous 15 years.

The odds ratio for breast cancer, adjusted for age, parity, family history, education, and previous benign breast disease, was 0.55 (95% CI 0.32–0.94) for any overnight shift work and 0.64 (95% CI 0.28–1.45) for overnight shift work but no evening shift work. The corresponding crude odds ratio estimates were 0.53 (95%CI 0.32–0.88) and 0.57 (95% CI 0.26–1.25), respectively. The adjusted odds ratios decreased by duration of overnight shift work (only periods with >1 night shift/week were included) and an odds ratio of 0.32 (95% CI 0.12–0.83) was found for the longest exposure category (≥8 years). The odds ratio for breast cancer following evening shift work was 1.21 (95% CI 0.90–1.64), but, according to the melatonin hypothesis, evening work should not be a risk factor for breast cancer (1).

Schwartzbaum et al (9) analyzed all major cancer sites in a cohort study of all gainfully employed inhabitants of Sweden (≥20 hours/week) included in the 1960 and the 1970 censuses. Altogether 3% of the men and 0.3% of the women were classified as shift workers (69 759 men and 3057 women). Among them, 6792 incident cases of cancer were identified in the national cancer register during the follow-up period, 1970–1989. The classification of shift workers relied on a job-exposure matrix constructed from a survey of living conditions in 1977–1981. Shift workers were defined by occupation–industry combinations recorded in the censuses with at least 40% working rotating shifts with three or more possible shifts per week or working any hour between 1300 and 0400 at least 1 day per week. The most common exposed occupations were paper and paperboard worker, paper pulp worker, furnace worker, fire fighter, policeman, civilian protective service worker, and railway engine driver among the men and crane and hoist operator, delivery woman in the paper and printing industry and midwife among the women. The reference

population was occupation–industry combinations with <30% shift workers.

The observed number of breast cancer cases was close to the expected [standardized incidence ratio (SIR) 0.94, 95% CI 0.74–1.18]. This was also the case when the analyses were restricted to workers employed in a job classified as shift worker in both 1960 and 1970 and when only workers of jobs with >70% shift workers were classified as exposed.

Prostate cancer. *Kubo et al* (7) studied 14 052 men working between 1988 and 1990 and followed them until 1997. In a self-administered questionnaire, the participants were asked which work schedule they had been engaged in the longest. Altogether 20% reported fixed or alternate night and day work. Incident cases of prostate cancer (ICD-10 C61, N=31) were identified by linkage with several regional cancer registers. The analyses were adjusted for a long list of potential confounders, and the reference was daytime work. The study showed relative risks of 2.3 (95% CI 0.6–9.2) for fixed night work and 3.0 (95% CI 1.2–7.7) for alternate night and day work. No analyses were conducted for the duration of nightshift work.

Conlon et al (8) utilized previously collected population-based case–control data to assess a possible association between shift work and prostate cancer. A total of 760 cases recorded with a cancer register diagnosis of prostate cancer and 1632 controls reported their lifetime work history and, for each job lasting ≥1 years, described the usual worktime as "daytime shift, evening or night shift, rotating shift, other". The participants were classified as ever having worked full-time rotating shifts (excluding those working part-time rotating shifts) and according to the duration of this work. Among the controls, 44% reported ever working fulltime-rotating shifts. The analyses were adjusted for age and family history of prostate cancer. The odds ratio for prostate cancer was 1.19 (95% CI 1.00–1.42) for ever working rotating shifts. There was no trend by years of rotating shifts (P-value = 0.42).

Schwartzbaum et al (9) reported no increased risk of prostate cancer (SIR 1.04, 95% CI 0.99–1.10). Further details of this study were presented earlier in this review.

Colon cancer. *Tynes et al* (33), in addition to detailed results for breast cancer, reported standardized incidence ratios for the most frequent cancer sites among all radio and telegraph operators using the background population as reference and showed a nonsignificantly increased risk for colon cancer (SIR 1.3, 95% CI 0.6–2.6). Further details of this study were presented earlier in this review.

Schernhammer et al (23) studied the risk of colon and rectum cancer following rotating nightshifts in the US Nurses' Health Study, and the study population was almost identical to the population of Schernhammer et al's in 2001 (22). The participants with ulcerative colitis, Chron's disease, or familial polyposis syndrome, in addition to a previous cancer (except nonmelanoma skin cancer), were excluded, and the population then comprised 78 586 participants. Information on nightshift work was identical to the information of the 2001 study. The analyses were adjusted for an extensive list of potential confounders and showed that women who worked 1–14 or ≥15 years on rotating night shifts had relative risks of 0.93 (95% CI 0.74–1.17) and 1.32 (95% CI 0.93–1.87), respectively, for colon cancer. A test for trend showed a P-value of 0.20. When rectal cancer was included in the case category, a similar pattern was found, but the trend test reached statistical significance (P-value = 0.04).

Schwartzbaum et al (9) reported no increased risk of colon cancer (SIR 1.03, 95% CI 0.94–1.13).

All cancer. *Taylor et al* (4) included 4188 male workers employed for at least 10 years in shift work in, for example, coal, brick, metal, and vehicle manufacturing in a retrospective cohort study in 1956 to 1986. Altogether 45% worked three-shift weekly rotating shifts, 35% worked three-shift rapid rotating shifts, and 19% worked alternate days and nights. A total of 722 died during the follow-up, and 219 died from cancer, while 188.8 deaths were expected according to the age- and calendar-year-adjusted national rates, P-value <0.05. This value corresponds with a standardized mortality ratio of 1.16. Results were also presented for ex-shift workers who did not fulfill the 10-year night shiftwork criterion; the standardized incidence ratio was then 1.12 (29 observed cancer deaths).

Rafnsson et al (5) conducted a retrospective cohort study of 211 men employed in a fertilizer plant for at least 1 year in 1954–1985 and followed them until 1985. They all worked three shifts according to payroll information, and 34 died during the follow-up, 14 due to cancer, while 9.98 deaths were expected from the national rates. The mortality decreased as the years of shift work increased.

Tynes et al (33) reported a standardized incidence ratio of 1.2 (95% CI 1.0–1.4) for all cancer among all radio and telegraph operators using the background population as reference.

Schwartzbaum et al reported a marginally increased overall cancer risk of statistical significance among workers classified as nightshift workers (SIR 1.02, 95% CI 1.00–1.05) (9).

Contributory evidence

Light at night at home and latitude of residence. Some epidemiologic studies have suggested that light at night at home is associated with breast cancer. Davis and

his colleagues (32) showed an increased risk among women who did not sleep when the nocturnal melatonin peak typically occurs, and O'Leary et al (6) found an increased risk among women who frequently turned on the light at home during sleep hours. However, both studies relied on self-reported retrospective information about light exposure, and information bias was a likely explanation for the findings. Lower breast cancer incidence has been reported in the arctic region, and it has been hypothesized that lower light exposure during wintertime may at least partly be a causal link (65).

Pilots and flight attendants. Flight attendants have an increased risk of breast cancer, and it has been suggested that this increment is related to exposure to light at night (3). However, the studies published so far have not assessed nightshift work specifically. Pukkala et al (81) reported an increased incidence of prostate cancer among male airline pilots that increased as the number of long-haul flights (expected to include nightshift work and jet lag) increased, but the risk also increased as the dose of cosmic radiation increased, whereas the all-cancer and colon-cancer incidence did not exceed the expected numbers. In a large European study of airline cabin attendants, mortality from all cancers and large-intestine cancer was lower for both genders than for the background population (82). Mortality from breast cancer was slightly increased among the women but showed no trend by duration of employment. Rafnsson et al (83) reported an increasing risk of breast cancer as the length of employment increased among Icelandic cabin attendants flying long-haul international flights in the pre-jet period, but no trend was evident after jet planes were introduced. Kojo et al (68) showed no evidence that the risk of breast cancer increased as the number of long-haul flights increased among Finnish female cabin attendants.

Cancer risk and melatonin in the visually impaired. The risk of breast cancer and possibly also prostate cancer seems to decrease as the degree of visual impairment increases (84). Blind persons may show abnormal melatonin rhythms (85), but the level of melatonin output during a 24-hour period, measured by 6-sulphatoxymelatonin, does not correlate with the level of visual impairment (86, 87).

Melatonin level and risk of breast cancer. In a prospective study, urinary concentrations of 6-sulfatoxymelatonin in 24-hour urine samples did not differ between breast cancer patients and their controls (88), while, in another prospective study, the odds ratio for breast cancer declined as the levels of 6-sulfatoxymelatonin increased in morning urine samples (76). These two studies are the only prospective studies published on this issue so far.

Biological mechanisms. Originally, it was hypothesized that light at night could suppress melatonin output and increase estrogen levels and thereby increase the risk of breast cancer, but, at present, it is unclear if light at night or melatonin affects estrogen levels in humans (2). Melatonin has been shown to have an oncostatic effect on chemically induced tumors with an increased tumoral latency (the time elapsing from the administration of the carcinogen and the appearance of palpable mammary tumors) among rodents, and constant light has stimulated tumorigenesis in rats, but not in all studies (36, 55). In a frequently cited study by Blask et al (89), constant light increased the growth of a human breast cancer xenograft implanted into a nude rat model. Melatonin has also been proposed to act as an antiestrogen, to enhance immune function, and to have antioxidant properties (90). Anderson et al (91) reported a significant reduction in the number of breast tumors among female rats that were exposed to constant light from the age of 26 days on, and this result was in contrast to earlier findings from rats exposed to constant light beginning before birth. In addition, Stevens (2) has hypothesized that light exposure in utero may increase breast cancer risk.

Discussion

Overall findings

Years of nightshift work was the principal measure of exposure analyzed across the studies in this review, except for the studies authored by Kubo et al (7) and Taylor et al (4). Three studies reported a significantly increased risk of breast cancer for long-term nightshift work beyond 20–30 years (22, 24, 34). Virtually no effects were found for shorter durations. The two studies by Hansen (25) and Davis et al (32) showed a small influence of duration of employment on the risk of breast cancer, but these authors defined long-term shift work as 3 or ≥6 years, respectively. However, both studies reported an increased risk of breast cancer in the overall analyses (ever versus never) of statistical significance. O'Leary et al (6) showed a negative trend for increasing years of nightshift work (no statistical testing of the trend was presented). Others reported trend tests of statistical significance for duration of nightshift work (22, 32, 34). However, these tests have to be interpreted with caution since increased risks in single categories may have influenced the P-values heavily. Furthermore, it was not always clear if the tests were based on the original continuous exposure data or on the categorical classification (eg, the midpoint values).

Tynes et al (33) observed an increasing risk for breast cancer for those above 50 years of age but not for those below this age; this finding was not replicated by Lie et al (34). Shernhammer et al (22) reported comparable

risks for premenopausal and postmenopausal nurses, and menopausal status probably does not modify the risk of breast cancer following nightshift work.

Kubo et al (7) and Conlon et al (8) indicated increased risks for prostate cancer for both fixed and rotating night shifts, but the cases were few or the effect was only marginal. Schernhammer et al (23) reported an increasing risk of colon cancer as the duration of rotating night shifts increased, and this finding was supported by the slightly increased standardized incidence ratio observed by Tynes et al (33) for all radio and telegraph operators. However Schwartzbaum et al (9) observed no increased risk of colon cancer. The occurrence of all cancer was close to the expected values in the four studies that analyzed this outcome (RR 1.0–1.2) (4, 5, 9, 33). A negative exposure–response relationship was indicated in the only study that assessed the duration of shift work, and this finding does not support a causal effect due to occupational factors (5).

Study populations and design

Of the 13 studies, 6 were based on the general population, 4 studied nurses (three independent populations), 2 studied industrial workers, and 1 studied radio and telegraph operators.

It was noted that the 3 studies indicating a long-term effect of nightshift work on breast cancer risk were all conducted among nurses (22, 24, 34). Four studies (three populations) used a prospective cohort design (7, 22–24), four were register-linked studies (9, 25, 33, 34), three were case–control studies (6, 8, 32), and two were retrospective cohort studies linking personnel records and mortality data (4, 5).

Cancer outcome

Cancer diagnoses relied on cancer register data, weekly reports from diagnosing institutions, medical records, and death certificates and were expected to have high specificity in all of the studies and to be unrelated to exposure status. The identification of cases in the three studies of Schernhammer et al (22–24) did, however, rely partly on self-reports and may have been affected by nightshift status, but this possibility is less likely.

Nightshift work

O'Leary et al (6) defined nightshift work the most precisely. The definition of Davis et al (32) was less specific and did not request that the shift last overnight. Schernhammer et al (22), Kubo et al (7), and Conlon et al (8) did not request that the participants consider the timing or duration of their nightshift work during the day.

O'Leary et al (6) and Davis et al (32) classified the participants as exposed in the principal analyses if they had experienced one nightshift per week or more, which corresponds well with the 3 days per month criterion applied by Schernhammer et al (22).

Schernhammer et al (22) did not include nurses working fixed (permanent) night shifts in their exposed category. If fixed nightshift workers have an increased risk of breast cancer and furthermore were classified as unexposed, the results would be biased towards the null. If, on the other hand, fixed nightshift workers have no increased risk, there would be inconsistent findings if the cumulative number of nightshifts is the relevant exposure metric. No increased risk of breast cancer for the fixed nightshift workers could also have been the finding because these workers adopt an altered circadian rhythm and melatonin is less strongly suppressed. But this is not a likely possibility since fixed nightshift workers are expected to return to a normal diurnal rhythm during weekends and days off. Under all circumstances, we would have appreciated having results for both rotating and fixed nightshift workers.

Given the low prevalence of workers on fixed nightshifts among all nightshift workers [0.4% versus 20% (18)], it was expected that the reviewed studies mainly analyzed the effect of nonfixed (or rotating) nightshift work, even if they did not specify such. One exception is the study by Kubo et al (7) that reported results for fixed nightshift work. The present database thus does not allow any assessment of a possibly different risk profile for fixed night shifts.

In the population-based studies, the prevalence of nightshift work was 3% for the men and 0.3% for the women in the study by Schwartzbaum (9), 5% for the women in the studies of Davis et al (32) and Hansen (25), and 20% and 44%, respectively, in the studies by Kubo et al (7) and Conlon et al (8). These differences probably reflect different work conditions across the study populations. They also reflect the different definitions of nightshift work used, and the very low prevalence in the study by Scwartzbaum et al (9) may cause the validity of their classification scheme to be doubted.

As expected, the cut-off levels used to define increasing levels of nightshift work differed across studies, but it was noted that this approach was also the case for the three studies authored by Schernhammer et al (22–24). It would be of interest to see all of the results lined up according to the same cut-off points.

Information about nightshift work was obtained retrospectively in the three case–control studies (6, 8, 32), and thus the reporting may have been influenced by case status. However, shift work is easily estimable, and information bias probably has not been a major concern. On the other hand, selective recall may have significantly affected the results for ambient light levels at night in homes.

In the four register-linked studies, nightshift work was assessed on a group level (ship, industry, type of

hospital department, and occupation–industry combinations) and thus represented estimates of the likelihood of nightshift work (eg, an estimated 40% of the participants classified as exposed in the study by Hansen were not involved in nightshift work) (25). Lie et al (34) and Tynes et al (33) did not assess the degree of misclassification of nightshift work, and Tynes et al did not differentiate between evening shifts and night shifts. Schwartzbaum et al (9) apparently included an unknown proportion of workers on evening shifts in the exposed category of their principal analyses. More than 60% of the workers of this study classified as exposed were furthermore not engaged in shift work. These studies compared ships, hospital departments, occupations, and industries, which are proxy measures of nightshift work that may have low specificity. Such misclassification of exposure is expected to be nondifferential with respect to cancer status and thus will bias true associations towards the null. On the other hand, it is likely that such rather broad proxy measures may be proxies for other exposures and not only nightshift work. The Hansen study (25) exemplifies this possibility by showing that the manufacture of beverages, land transport services, catering, and air transport services (proxies for nightshift work) are also proxies for alcohol consumption. The results of these studies thus may have been confounded in any direction and not necessarily towards the null. On the other hand, these studies are robust with respect to information bias and selection bias due to the complete register data from independent sources.

Nightshift work per se is not expected to be a risk factor for cancer; but is, instead, a surrogate measure for, for example, light at night or circadian phase shift or is an influence on an intermediary risk factor (eg, sleep deprivation, diet or lifestyle that is causally related to cancer). In any case, one would expect that cancer risk increases as the cumulative number of nightshifts increases, regardless of whether this work entails fixed nightshifts or rotating nightshifts. Workers with fixed nightshifts are expected to accumulate a higher number of shifts than rotating nightshift workers, and excluding them from the analyses would thus reduce the power to detect a true effect. In line with this reasoning, Kubo et al (7) showed slightly higher risks of prostate cancer for fixed nightshift work than for rotating nightshift work. It would therefore be of interest to have data presented for the fixed nightshift workers of the Nurses Health Study II (24) and also data based on the lifetime working histories of Davis et al's study (32).

It has been argued that workers on rotating or mixed night shifts should have the highest cancer risk because they do not retrain to an altered circadian rhythm (22). However, a large field study of the melatonin profile of nightshift workers showed lower melatonin concentrations in fixed nightshift workers than in mixed nightshift workers (29). Offshore workers working 2 weeks on 12-hour night shifts adapted to an altered circadian rhythm and showed rates of phase shifts of 1–2 hours per day (92). However, we have not been able to identify field studies of melatonin profiles among nurses or others working a limited number of nights per week that documented that mixed or rotating nightshift workers have more irregular circadian phases than day workers or permanent nightshift workers.

Confounding

There is evidence indicating that the nightshift workers included in this review more often smoked, had a higher body mass index, and less often had hormone replacement therapy than dayshift workers. Smoking is not an independent risk factor for breast cancer but may be a proxy for other factors related to lifestyle and socioeconomic status that may be risk factors for breast cancer (16). The inverse relationship between socioeconomic status and breast cancer risk does not, however, support this argument (93). A higher prevalence of women with early menarche was indicated among nightshift workers, but they generally showed no consistent differences when compared with day workers observed with respect to reproductive factors; however, the differences were found within individual studies that should be accounted for in the adjusted analyses.

The workers classified as nightshift workers in the Hansen study consumed up to six times more alcohol than the day workers (3.5–6.0 drinks/week versus 1.1 drinks/week), but alcohol can only explain a few percent of the observed increased risk of breast cancer (16) and has barely confounded the results significantly.

The three studies that suggested an effect of long-term nightshift work were all conducted among nurses (22, 24, 34). On one hand, this similarity may have been a strength because extraneous risk factors are expected to be less of a problem in analyses relying on comparisons within a profession. On the other hand, this likeness may also have been a major limitation since these nightshift nurses may have shared common, yet unknown, risk factors other than nightshift work, and I would have felt much more confident if the results had been replicated across different occupations and industries.

Confounder control was limited in the four register-based studies because routine register data on, for example, body mass index, oral contraceptive use, hormone replacement therapy, and age at menarche and menopause were not available (9, 25, 33, 34). Several studies did not control for oral contraceptive use or hormon replacement therapy, and Schernhammer et al were the only ones to adjust for alcohol consumption (22–24). Still it has to be emphasized that no strong confounding effect was indicated by the studies of Schernhammer et

al (22, 24) or O'Leary et al (6), who presented crude risk estimates in addition to the adjusted estimates.

One also has to bear in mind that, if alcohol or smoking habits or other cancer risk factors are influenced by nightshift work (act as intermediary risk factors), adjusting by these factors may blur causal relationships.

Selection bias

The participation rates were generally high in all of the studies, and selective study participation is not expected to have influenced the findings significantly, especially in the case of the register-linked studies with almost complete data. The Davis et al study (32) may be an exception, since these authors identified controls by random-digit dialing that may possess specific problems when nightshift work is studied, since night working controls may not be reached by telephone as often as day workers.

On the other hand, selective reporting of findings within the individual studies may have influenced the overall risk pattern obtained for nightshift work. For instance, Schernhammer et al (23) presented results for colon and rectal cancer but not for other cancer sites even if they argued in favor of a general effect on the tumorigenesis of light at night, and this information was collected in the Nurses Health Study (94). Furthermore, Schernhammer et al (24) and Conlon et al (8) obtained data on fixed shift work, and Davis et al (32) collected data on lifetime nightshift work, but none of them presented the findings for these exposure measures. Hansen (25) left workers of industries with an estimated 40–60% nightshift workers out of the analyses. Schwartzbaum et al (9) did the same to those with 30–40% shift workers. If the decisions as to whether results should be presented or not were made a priori, the results should not have been affected. But if the decisions were data driven, the collective risk pattern might have been biased. I am, of course, aware that numerous decisions have to be made when data are extracted, analyzed, and presented, and much information must be left out due to parsimonious results and clear conclusions. However, I would have appreciated it if these decisions had been more thoroughly described and the nonpresented results briefly mentioned.

Contributory evidence

The supportive database in favor of a causal association between light at night and breast cancer is large, but still there are numerous conflicts. Animal experiments have documented significant oncostatic effects of melatonin, and constant light exposure stimulates mammary carcinogenesis. But it has been emphasized that results based on nocturnal animals should only be generalized to diurnal humans with caution (40). Furthermore, one may question whether the exposure models are valid for nightshift work. Thus it is uncertain to what degree the results can be extrapolated to humans working night shifts.

Nightshift workers have lowered melatonin levels during night shifts and may adapt to an altered circadian rhythm during longer periods of nightshift work, but the total 24-hour melatonin output is apparently not significantly affected by nightshift work, at least among nurses (the profession most extensively studied for breast cancer risk) working mixed and fixed night shifts. Airline crew are expected to experience jet lag and nightshift work during long-haul flights and have an increased risk of breast cancer, and possibly also of prostate cancer. But data based on individual flight histories are sparse and equivocal.

The three positive studies of breast cancer were restricted to nurses (22, 24, 34). A high proportion of nurses work rotating night shifts (22, 24). Register-linked studies present increased risks of breast cancer in the nursing profession (95–101), but case–control studies that include information on reproductive factors or other potential confounders are in general negative (102–106).

Blind persons that may have lower sensitivity to light exposure have a decreased risk of breast cancer, and this occurrence is in line with a cumulative effect of light at night (and nightshift work). But this finding is not in line with the circadian disruption hypothesis because many visually impaired persons have free running cycles, and, furthermore, it is not clear whether blind persons secrete more melatonin than people who can see. Studies of light at night at home are supportive of a causal effect of nightshift work, but vulnerable to information bias, and thus have to be interpreted carefully.

Only two prospective studies of melatonin level and cancer risk have been conducted, and they present conflicting results. No data are currently available showing such an effect for instable melatonin rhythms.

Previous literature reviews

I identified 26 previous reviews or hypothesis papers about nightshift work, light at night, and the risk of cancer. The conclusions were generally in line with that of Megdal et al (3): "In summary, this meta-analysis suggests that shift work, including work as a flight attendant, increases the risk of breast cancer by 48% [p 2031]"; Hansen (45): ". . . there is so far relative consisting evidence that working non-day time may increase the breast cancer risk among females [p 534]"; and Davis et al (43): "Collectively these findings provide intriguing evidence that suggest working at night, or in occupations characterized by night shift work, may be associated with an increased risk of cancer [p 540]". Anthony Swerdlow (107) was more careful in his conclusion: "Hence, the possibility that shift work per se increases the risk of

breast cancer cannot be dismissed, but on the other hand it remains possible that the apparent associations are due to confounding [p 18]". None of these reviews included the papers published in 2006 and 2007 by O'Leary et al (6), Kubo et al (7), Conlon et al (8), and Schwartzbaum et al (9) that are included in this review.

Concluding remarks

Five of the eight studies on breast cancer in women indicate increased risks. Three of the positive studies show significantly increased risks after 20–30 years of nightshift work. Hence there are indications of an effect of long-term nightshift work on breast cancer risk. Findings for shorter durations of nightshift work are inconsistent. There are several reasons for caution regarding the suggested long-term effect. The number of studies is small, the positive studies were all conducted for the same occupational group (nurses on nightshift), and the risk estimates are only moderately raised. These reasons make the results sensitive to bias, chance, and confounding, although I have not been able to pinpoint specific sources.

In conclusion, there is limited evidence for a causal association between nightshift work and breast cancer (+), while there is insufficient evidence of a causal association for prostate cancer (0), colon cancer (0), and overall cancer (0). An expert working group convened by the International Agency for Research on Cancer came to the same conclusion at their meeting in October 2007, that there is limited evidence for the carcinogenicity of shift work that involves night work among humans (108).

Nightshift work is prevalent, the incidence of breast cancer is high, and an even slightly increased risk may carry a heavy burden for public health. A wealth of new studies on the physiological and pathophysiological effects of environmental lighting and circadian disruption are expected to provide path-breaking new insights (109). Still, further epidemiologic studies of nightshift work and the risk of breast cancer, as well as of other health effects, are needed. These studies should especially focus on reliable exposure data obtained on an individual level and include a wide range of occupational groups.

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Appendix 1

Degree of evidence of a causal association between exposure to a specific risk factor and a specific outcome according to criteria of the Scientific Committee of the Danish Society of Occupational and Environmental Medicine

The following categories are used.

+++	strong evidence of a causal association	0	insufficient evidence of a causal association
++	moderate evidence of a causal association	–	evidence suggesting lack of a causal association
+	limited evidence 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 epidemiologic 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 epidemiologic 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 epidemiologic 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 a 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 epidemiologic 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, and the like.

Biological plausibility and contributory information may add to the evidence of a causal association.