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Night Shift Work and Risk of Breast Cancer

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Abstract
Purpose of Review Night work is increasingly common and a necessity in certain sectors of the modern 24-h society. The embedded exposure to light-at-night, which suppresses the nocturnal hormone melatonin with oncostatic properties and circadian disruption, i.e., misalignment between internal and external night and between cells and organs, are suggested as main mechanisms involved in carcinogenesis. In 2007, the International Agency for Research on Cancer (IARC) classified shift work that involves circadian disruption as *probably carcinogenic* to humans based on limited evidence from eight epidemiologic studies on breast cancer, in addition to sufficient evidence from animal experiments. The aim of this review is a critical update of the IARC evaluation, including subsequent and the most recent epidemiologic evidence on breast cancer risk after night work.
Recent Findings After 2007, in total nine new case-control studies, one case-cohort study, and eight cohort studies are published, which triples the number of studies. Further, two previous cohorts have been updated with extended follow-up. The assessment of night shift work is different in all of the 26 existing studies. There is some evidence that high number of consecutive night shifts has impact on the extent of circadian disruption, and thereby increased breast cancer risk, but this information is missing in almost all cohort studies. This in combination with short-term follow-up of aging cohorts may explain why some cohort studies may have null findings. The more recent case-control studies have contributed interesting results concerning breast cancer subtypes in relation to both menopausal status and different hormonal subtypes. The large differences in definitions of both exposure and outcome may contribute to the observed heterogeneity of results from studies of night work and breast cancer, which overall points in the direction of an increased breast cancer risk, in particular after over 20 years of night shifts.
Summary Overall, there is a tendency of increased risk of breast cancer either after over 20 years of night shift or after shorter periods with many consecutive shifts. More epidemiologic research using standardized definitions of night work metrics and breast cancer subtypes as well as other cancers is needed in order to improve the epidemiologic evidence in combination with animal models of night work. Also, evidence-based preventive interventions are needed.

Keywords Circadian disruption · Light-at-night · Breast cancer · Shift work · Melatonin

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Introduction

Working outside the hours with daylight from about 7 a.m. to 7 p.m. has become increasingly normal during the last 100 years. The invention of electrical lighting and the industrialization of Western countries in the late 1800s have facilitated this change of working life from solely the period with naturally lighted day period to also include evening, night, and early morning by use of artificial electrical light. Consequently, most work has moved from outdoor with bright natural light exposure to indoor with dim light conditions, including a narrower spectrum than natural daylight [1]. Currently, in the EU, about 22% of men and 11% of women work on shifts that include night work. Similarly in the USA, about 17% of full-time salaried men and 12% of women worked on shifts that included nights [2]. The most frequent sectors with night work are hospitals, hotels, transportation, security, and parts of industry that depend on a 24-h production 7 days a week, as well as modern societies in general expect 24-h activity [3, 4]. Shift and night work are complex exposures due to many different aspects that may characterize such exposure, including the direction of shifts (e.g., forwards (day, evening, night) and backwards (day, morning, night)), time of start and end, sequence of non-day shifts, work hours per shift, and rest periods between shifts [5]. Thus, Hall et al. in a recent study from Canada based on a survey of 88 companies observed over 400 different shift-systems [6].

From ancient time, the light on Earth has been determined by the planet's 24-h rotation about itself (morning, day, evening and night) and about the 365-days circulation around the sun (seasons). Consequently, over the 3 billion years evolutionary past, virtually all life on Earth from cyanobacteria to humans has adapted to the 24 h circle of light and dark. Thus, the timing and duration of the daily exposure to light is known as one of the most important determinants for circadian (24 h) rhythms (daily oscillation) in humans, animals, and other living species on the Earth [7, 8]. In humans and other mammals, the pineal gland hormone melatonin is the main biological signal which synchronizes the main time keeper, the suprachiasmatic nucleus (SCN) in the anterior hypothalamus, with local clocks in cells and tissue, and aligns the entire circadian system to the local environmental dark-light time of the 24-h day [9]. Normally, melatonin is only produced from dusk to dawn, and the amplitude and total daily production is strongly influenced by age, sex, chronotype (morning or evening preference), individual sensitivity, timing, duration, and history and spectrum of light exposure on retina during the day. In the event of exposure to light-at-night, e.g., during social activities or in particular work, melatonin is normally suppressed, and a phase shift may occur after several consecutive light-at-night exposures [10–13]. Melatonin has oncostatic properties in animal assays and has been shown to mediate pathways involved in cancer [14], including estrogens involved in breast cancer [15, 16]. Further, it has been shown in some prospective studies that women with the highest levels of metabolites of melatonin have a lower risk of breast cancer compared to women with the lowest levels [17, 18].

Three decades ago Richard Stevens was the first to hypothesize that exposure to light-at-night may suppress the pineal gland production of melatonin and in turn increase the risk of breast cancer [19].

In 2007, the International Agency for Research on Cancer (IARC), which is a part of the WHO, evaluated the evidence of shift work in relation to cancer. Due to the normal procedure by IARC, the evidence from epidemiology, animal experiments, and mechanistic studies were evaluated separately, and an overall synthesized conclusion was established [20]. Only eight epidemiologic studies (three cohorts and five case-control studies) on shift work and breast cancer were available for the 2007 evaluation. The strongest evidence came from two independent prospective cohort studies on nurses from the USA, showing significantly increased breast cancer risk after over 20–30 years of rotating night shift work [21, 22]. Additional support came from four case-control studies and several studies on flight attendants with increased breast cancer risk. The latter group may both have had night work and have crossed time zones, but results may at least partly be confounded from exposure to cosmic radiation [4]. A crude meta-analysis based on the longest category of night work exposure from six studies found a relative risk of breast cancer of 1.51 (95% CI, 1.36–1.68) [23]. Overall, the evidence for an association between night work and breast cancer was credible, but bias, confounding, and chance could not be excluded (i.e., limited evidence according to IARC criteria). Over 50 animal experiments were available representing different biological aspects of melatonin and light exposure, including animal "jet lag models," rather than "shift work models." In particular, Blask et al. conducted a novel experiment where nocturnal light exposure was shown to decrease melatonin levels and to progress the growth of human breast cancer cells in rat models [24, 25]. Overall, there was sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night). Furthermore, experimental data supported that similar biological mechanisms occur both in animals and humans on molecular, cellular, and systemic level [26]. Taking all the evidence together, it was concluded that shift work that includes circadian disruption is probably carcinogenic to humans [27]. Subsequently, it became possible in Denmark as the only country so far to get breast cancer after long-term night shift work acknowledged as an occupational disease and get economical compensation [28].

The 2007 evaluation by IARC apparently stimulated epidemiologic research on shift work and cancer. Although there have been some studies on shift work and other cancer sites than breast cancer, in particular prostate and colorectal cancers, relatively few studies have addressed these cancers compared to breast cancer. Therefore, an overall evaluation of other cancers than breast cancer is somewhat in its early phase due to the lack of epidemiological studies.

The main aim of the present review is to describe and evaluate studies on night work and risk of breast cancer that have been published since the IARC evaluation in 2007.

Assessment of the Night Shift Work Exposure

Accurate assessment of exposure is normally the Achilles' heel in all epidemiologic studies and inaccurate exposure may bias results. All studies on shift and night work and breast cancer risk have used different definitions of the exposure, and partly adjusted for different potential confounders, which was one of the limitations of the epidemiological studies noted at the 2007 IARC evaluation [2]. Therefore, an international group of epidemiologists gathered for a workshop at IARC in 2009 and suggested standardization of variables used in future studies [29]. In particular, it was suggested that studies should capture at least "1) shift system (start time of shift, number of hours per day, rotating or permanent, speed and direction of a rotating system, regular or irregular); 2) years on a particular non-day shift schedule (cumulative exposure to the shift system over the subject's working life); and 3) shift intensity (time off between successive work days on the shift schedule)" [29]. Despite these recommendations, all of the recent studies on night work and cancer have used different definitions of night work concerning both the period of work within the 24-h day and the intensity of night work, i.e., consecutive working nights and periods of rest in between. Thus, many studies, including all existing cohorts use only number of years of night shift as a surrogate for dose, irrespectively that most persons do not have night work every day of the year. This inaccurate assessment of the extent of night work may underestimate risks because of the obvious different impact, within the span from a few to 31 nights per month, on physiology and thereby potentially the breast cancer risk. One exception is a large register-based cohort from Denmark based on all employees in public hospitals where objective payroll data, including time of start and end of each shift, is available from 2007 to 2012 on an individual level [30]. Because of the potential for linkage with many health-related registries in Denmark [31], this cohort will be very valuable in future decades when sufficient follow-up time for cancer becomes available.

The intention in most definitions of night work that are used in epidemiological studies of cancer is to focus on exposure to electrical light during the period of the night where melatonin normally peeks, i.e., during about 2–3 a.m. [32, 33]. A recent study, including employees mainly at hospitals showed that the proportion of shifts classified as night shifts in practice differs little in Denmark when night shifts are based on definitions including a period during the night (i.e., working time after midnight) [30]. Thus, the critical issue concerning definition of night shifts may rather be the number of consecutive night shift, e.g., during a week, which have different physiological impact on circadian disruption and cancer risk [34–36].

Differences in exposures to intensity and wavelength of the light, which may be very different in different occupational settings, also influence the level of melatonin suppression during the night [37, 38••]. Furthermore, individual differences in diurnal preference, which seems partly under genetic influence, result in melatonin peaking earlier for people with morning preference and later than average for people with evening preference [39–44]. Thus, the genetic component of diurnal preference or chronotype seems associated with breast cancer risk [32] via a polymorphism in the circadian gene *PER3* [45] [46]. One relatively small case-control study has shown that both women with morning and evening preference have an increased risk of breast cancer associated with night shift work, but the risk is highest for women with morning preference [47]. This has, however, yet to be confirmed in larger studies.

Information on working time is normally obtained by self-reports from study participants, which potentially may be inaccurately obtained by questionnaires or interviews both in cohort and in case-control studies. Härmä et al. has recently compared objective information on working time from payroll data with questionnaire-based data on working time. Overall, there was a good correlation between self-reported shift work with night work, and permanent night shift (sensitivity and specificity over 90%), whereas shift work without night work had moderate validity (sensitivity 62%; specificity 87%). If this can be generalized to other studies, this means that self-reported information on night work in general may be valid, but may underestimate the effects in shift work without night shifts [48].

New Epidemiologic Evidence After the 2007 IARC Evaluation

In total, nine case-control studies [47, 49–56], one case-cohort study [57], and eight cohort studies have been published since the IARC evaluation [58–63]. Results and descriptive characteristics of the 18 new studies are shown in Tables 1 and 2. Including the eight studies available at the IARC evaluation [21, 22, 64–69], in total, 26 studies of night shift work and breast cancer were published in scientific journals by the end of 2016. A recent update, including 14 years of extended follow-up of two independent studies based on Nurses Health cohorts [21, 22] originally issued in 2001 and 2006, were published in early 2017 [70••].

Cohort Studies

All of the existing cohort studies, including those published prior to the 2007 IARC evaluation, were designed for other purposes than studying the association between night work and breast cancer. Thus, information on night work in all these studies is limited to relatively crude and imprecise questions on night work, which most often have been obtained several years after the establishment of the cohorts. Thus, at its best, they have information on duration of night work, but not on intensity, e.g., number of shifts during a week or month.

Table 1 Cohort studies of night work and breast cancer risk published after the IARC evaluation in 2007

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work					Cumulative night shifts (intensity)				
			Exposure categories	No. of cases	RR* adjusted	95% CI	p-trend	Exposure categories	No. of cases	RR* adjusted	95% CI	p-trend
Pronk et al., 2010, China	Prospective cohort (2000–2007)	(a) Job exposure matrix score (0–3) for likelihood of night shift work b) Self report (2002–2004): starting work after 10 pm at least 3 times a month for over 1 year	(a) 0	423	1	Reference		(a) 0	423	1	Reference	0.84
			>0–≤14 years	108	1.1	0.9–1.3		>0–≤34	102	1.0	0.8–1.3	
			>14–≤25 years	89	0.9	0.7–1.1		>34–≤66	103	1.0	0.8–1.2	
			>25 years	97	1.0	0.8–1.3	0.72	>66	89	1.0	0.8–1.2	
			(b) 0	276	1	Reference	0.26	(b) 0	276	1	Reference	0.17
			>0–≤5 years	25	0.9	0.6–1.3		>0–≤576	27	0.9	0.6–1.3	
			>5–≤17 years	29	0.9	0.6–1.4		>576–≤1632	28	1.0	0.7–1.5	
			>17 years	19	0.8	0.5–1.2		>1632	18	0.7	0.4–1.1	
Knutsson et al., 2012, Sweden	Prospective cohort of workers (WULF). Follow-up 1992–2008, 49,973 person-years	Day if working only day time at baseline, 1992–1995, and at follow-up in 1996–1997 and 2009	Day work	63	1	Reference	ND					
			Shift work without night	20	1.23	0.70–2.17						
		Shift work without night work ≥1 occasion (1992–1995, 1996–1997, and 2009) Shift work with night work (22:00–06:00) ≥ 1 occasion (1992–1995, 1996–1997, and 2009)	Shift work with night	14	2.02	1.03–3.95						
Koppes LL et al., 2014, Netherlands	Cohort study of 285,723 women with a paid job for at least 12 h per week. Obtained from the 14 Dutch Labor Force Survey (1996–2006). Follow-up from 1996 to 2009	Baseline questionnaire: do you work at night, meaning between midnight and 6 am: (a) no, (b) sometimes, and (c) regularly. No information on duration or intensity of shift-work	Never	2312	1	Reference	ND					
			Overall	219	0.87	0.72–1.05						
			Occupational (nurses)		1.42	0.92–2.19						
			Regular (nurses)		0.93	0.66–1.31						
			Occupational (non-nurses)		0.96	0.76–1.21						
			Regular (non-nurses)		0.87	0.68–1.11						
Åkerstedt et al., 2015, Sweden	Swedish twin cohort study (1998–2003). 13,656 female study participants from Swedish Twin Registry	Baseline questionnaire: "For how many years have you had working hours that meant that you worked nights at least now and then."	No night work	354	1	Reference	ND					
			Ever night work	109	0.94	0.73–1.22						
			1–5 years	57	0.92	0.65–1.29						
			6–10 years	16	0.79	0.45–1.37						
			11–20 years	18	0.77	0.43–1.38						
			21–45 years	18	1.68	0.98–2.88						
Travis et al., 2017, UK	Million woman study. Participants are women invited for breast cancer	Ever regularly worked at night: any time between midnight and 06:00 h, for at least three nights per month	Never worked at night	4136	1	Reference						
			Ever	673	1.00	0.92–1.08	0.68					
			<10 years	400	0.93	0.83–1.03						

Table 1 (continued)

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work: Exposure categories	No. of cases	RR* adjusted	95% CI	p-trend	Cumulative night shifts (intensity): Exposure categories	No. of cases	RR* adjusted	95% CI	p-trend
	screening. Established 1996 to 2001	Information on shift work obtained from survivors during the period 2009–12	10–19 years	140	1.14	0.96–1.35						
			≥20 years	89	1.00	0.81–1.23						
Travis et al., 2017, UK	EPIC-Oxford study, recruited around the UK 1993–1999	Regular work at night, or on night shifts or on call at night for at least one night per month or 12 nights per years. Information on shift work was obtained from survivors in 2010	Never worked night shifts	153	1	Reference	0.75					
			Ever	28	1.07	0.71–1.62						
			<10 years	15	1.18	0.69–2.01						
			10–19 years	11	1.92	1.03–3.57						
			≥20 years	1	0.22	0.03–1.61						
Travis et al., 2017, UK	UK Biobank, prospective cohort including 251,045 women enrolled 2006–10 across the UK. Response rate 5.5%	In current job working through the normal sleeping hours, e.g., 12 a.m. to 6 a.m.: never/rarely; sometimes; usually, always, do not know, prefer not to answer. Information on night work obtained at study baseline	Never/rarely night shift work at recruitment	2653	1	Reference	ND					
			At least sometimes	67	0.78	0.61–1.00						
Vistisen et al., 2017, Denmark	Danish register-based cohort of 155,540 female public health, primarily hospital employees. Work schedule from 2008 to 12. No information on work, including working time prior to 2007	Night work: ≥3 h between midnight and 5:00 h. Day work: > = 3 h between 06:00 and 20:00		751	1	Reference	0.10	Only day	751	1	Reference	0.10
				425	0.90	0.80–1.01		Ever non-day, non-night	69	0.94	0.73–1.20	
								1–5 nights	102	0.88	0.71–1.20	
								6–23 nights	98	0.87	0.70–1.08	
								24–67 nights	106	0.99	0.80–1.21	
								68–1325 nights	109	0.85	0.70–1.04	
								Ever night	425	0.90	0.80–1.01	

Table 2 Case-control studies of night work and breast cancer risk published after the IARC evaluation in 2007

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work					Cumulative night shifts (intensity)				
			Exposure categories	No. of cases	RR[a]	95% CI	p-trend	Exposure categories	No. of cases	RR[a]	95% CI	p-trend
Pesch et al., 2010, Germany	Population-based case-control (2000–2004)	Working the full-time period between 24.00–05:00 h for at least 1 year	Employed, never shift work	698	1	Reference	ND	Employed, never in shift work	698	1	Reference	
			Ever in night shift	55	0.9	0.6–1.5						
			>0–4 years	15	0.7	0.3–1.5		<1056 night shifts	25	0.7	0.3–1.3	
			5–9 years	11	0.9	0.3–2.8		≥1056 night shifts	25	1.7	0.7–4.2	ND
			10–19 years	10	0.8	0.3–2.6						
			≥20 years	12	2.5	0.6–10.0						
Lie et al., 2011, Norway	Nested case- control study in cohort of nurses (1990–2007)	Permanent and rotating night schedules lasting from at least 12 p.m. until 6 a.m.	Never night work	102	1	Reference	0.17	Never night work	102	1	Reference	
			1–11 years	410	1.2	0.9–1.5		<1007 night shifts	396	1.2	0.9–1.6	0.24
			≥12 years	187	1.3	0.9–1.8		≥1007 night shifts	201	1.2	0.9–1.7	
								<5 years night shift				
								≥3 consecutive shifts	194	1.1	0.8–1.6	
								≥4 consecutive shifts	160	1.2	0.8–1.6	
								≥5 consecutive shifts	137	1.2	0.8–1.7	
								≥6 consecutive shifts	119	1.2	0.8–1.7	
								≥7 consecutive shifts	109	1.1	0.8–1.6	
								≥5 years night shift				
								≥3 consecutive shifts	278	1.1	0.8–1.5	
								≥4 consecutive shifts	131	1.4	0.9–1.9	
								≥5 consecutive shifts	74	1.6	1.0–2.4	
								≥6 consecutive shifts	64	1.8	1.1–2.8	
								≥7 consecutive shifts	58	1.7	1.1–2.8	
Hansen and Stevens, 2011, Denmark	Nested case- control study in cohort of nurses (2001–2003)	Graveyard shift: about 8 h' work per day between 7 p.m. and 7 a.m. for at least 1 year Evening: before about 12 p.m. Night: after about 00 a.m.	Day, never evening and night	28	1	Reference	ND					ND
			Ever evening, never night	9	0.9	0.4–1.9						
			Ever after midnight, never permanent night	212	1.8	1.2–2.8						
			Ever permanent night	18	2.9	1.1–8.0						
			Day and evening	37	1	Reference	ND					
			1–5 years	55	1.5	0.9–2.5		Day-evening	37	1	Reference	
			5–10 years	70	2.3	1.4–3.5		<468 night shifts	63	1.6	1.0–2.6	
			10–20 years	66	1.9	1.1–2.8		468–1095 night shifts	80	2.0	1.3–3.0	
			≥20 years	39	2.1	1.3–2.3		≥1096 night shifts	87	2.2	1.3–3.2	
			Per year	267	1.02	1.01–1.03						
			Day	88	1	Reference	0.03	Day	82	1	Reference	0.02

Table 2 (continued)

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work: Exposure categories	No. of cases	RR[a]	95% CI	p-trend	Cumulative night shifts (intensity): Exposure categories	No. of cases	RR[a]	95% CI	p-trend
Hansen and Lassen, 2012, Denmark	Nested case- control study in cohort of military employees (1990–2003)	About 8 h's work per day between 5 pm and 9 am for at least 1 year	1–6 years	13	0.9	0.4–1.7		<416	9	0.8	0.4–1.9	
			6–15 years	18	1.7	0.9–3.2		416–1560	14	1.4	0.7–2.9	
			≥15 years	12	2.1	1.0–4.5		>1560	17	2.3	1.2–4.6	
Menegaux et al., 2012, France	Population-based case-control study (2005–2007)	Night: ≥ 1 h between 11:00 p.m. and 5:00 a.m. Late evening: ending between 11:00 p.m. and 3:00 a.m. Overnight: at least 6 consecutive work hours between 11:00 p.m. and 5:00 a.m. Early morning: starting between 3:00 and 5:00 a.m.	Never night	1068	1	Reference	ND	Never night	106	1	Reference	ND
			Ever night	164	1.27	0.99–1.64		Night				
			<4.5 years	66	1.12	0.78–1.60		<4.5 years and <3 shift/week	30	1.04	0.62–1.75	
			≥4.5 years	98	1.40	1.01–1.92		<4.5 years and ≥3 shift/week	36	1.19	0.73–1.95	
								≥4.5 years and <3 shift/week	54	1.83	1.15–2.93	
								≥4.5 years and ≥3 shift/week	44	1.10	0.71–1.69	
			Late evening	42	1.25	0.79–1.28	ND	Overnight				ND
			Early morning	9	0.90	0.36–2-21		<4.5 years and <3 shift/week	15	0.92	0.45–1.89	
			Overnight	120	1.35	1.01–1.80		<4.5 years and ≥3 shift/week	25	1.59	0.86–2.96	
			<4.5 years	47	1.27	0.83–1.94		≥4.5 years and <3 shift/week	49	2.09	1.26–3.45	
			≥4.5 years	55	1.40	0.82–1.59		≥4.5 years and ≥3 shift/week	31	0.91	0.55–1.50	
Grundy et al., 2013, Canada	Case-control study from Vancouver, British Columbia and Kingston, Ontario	Night and evening shift: ≥50% of time in jobs with such shifts	None	751	1	Reference	0.5					
			0–14 years	283	0.95	0.79–1.16						
			15–29 years	72	0.93	0.67–1.30						
			≥30 years	28	2.21	1.14–4.31						
		Years in jobs starting or ending between 11 p.m. and 7 a.m.	None	826	–		ND					
			<15 years	172	1.29	1.01–1.65						
			15–30 years	49	1.27	0.83–1.95						
			≥30 years	16	1.68	0.74–3.79						
Fritschi et al., 2013, Australia	Case-control study	Two stage data collection: (1) postal questionnaire, (2) telephone interview: "OccIDEAS" provided automatic assessment of probability of exposure:	Never	1404	1	Reference						
			Ever	381	1.16	0.97–1.28						
			<10 years	199	1.25	1.00–1.56						
			10–20 years	98	1.09	0.79–1.50						
			20+ years	84	1.02	0.71–1.45	ND					
		Graveyard shift (worked any number of hours between midnight and 05:00)	None	1476	1	Reference	0.04					
			Ever	309	1.22	1.01–1.47						
			Low	51	1.09	0.70–1.68						

Table 2 (continued)

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work					Cumulative night shifts (intensity)				
			Exposure categories	No. of cases	RR[a]	95% CI	p-trend	Exposure categories	No. of cases	RR[a]	95% CI	p-trend
		Phase shift (high if >4 nights of forward rotation or 6 nights of backward rotation; medium: 3–4 nights forward or 4–6 nights backward; low with 3 nights backward rotation (backward rotation: if no shift-pattern or >2 days off between finishing day and starting night-shift) Duration of exposure at medium and/or high level	Medium	177	1.24	0.97–1.57						
			High	81	1.25	0.90–1.75						
			<10 years	160	1.35	1.06–1.72						
			10–20 years	58	1.12	0.74–1.68						
			20+ years	40	0.96	0.58–1.61						
Papantoniou et al., 2016, Spain	Case-control study from 10 regions in Spain based on face-to-face interviews	Partly and entirely working between 00:00 and 6:00 a.m. at least three nights per month. Reference group consists of woman who had never worked at night, including workers with until 2 night shifts per months and house wives	Never night work	1438	1	Reference		Never night work	1438	1	Reference	
			Ever night work	270	1.18	0.97–1.43		Cumulative number Total night shifts				
			1–4 years	67	1.21	0.83–1.76		36–599	62	1.15	0.80–1.64	
			5–14	103	1.13	0.83–1.53	0.176	600–1799	53	1.20	0.85–1.70	
			≥15	97	1.21	0.89–1.65		≥1800	56	1.18	0.83–1.69	0.248
			Ever permanent night work	114	1.19	0.89–1.60		Permanent night shifts				
			1–4 years	32	1.00	0.59–1.66		36–599	14	0.96	0.50–1.85	
			5–14	46	1.17	0.74–1.87		600–1799	16	1.15	0.65–2.04	0.149
			≥15	34	1.49	1.49–2.53	0.109	≥1800	20	1.48	0.81–2.68	
			Rotating night work	156	1.17	1.17–1.51		Rotating night shifts				
			1–4 years	40	1.58	0.94–2.66	0.369	36–599	14	1.34	0.77–1.67	
			5–14	56	0.96	0.65–1.41		600–1799	16	1.32	0.83–2.08	0.519
			> = 15	59	1.22	0.821.81		≥1800	20	1.08	0.66–1.79	
			Never shift work	1190	1	Reference						
			Permanent night	114	1.13	0.84–1.51						
			Rotating night	156	1.11	0.86–1.43						
			Rotating no night	93	0.78	0.57–1.05						
			Housewives	155	0.69	0.69–0.88						
Li et al., 2015, China	Case-cohort study of textile workers from Shanghai (1989–2000). 502 textile factories of which 100	Night shift is working between 24:00 and 05:00 h. In the 402 factories, 2 and 3 shift	0	557	1	Reference	0.095	0	557	1	Reference	0.155
			<12.8 years	286	0.99	0.83–1.17		>0–<1316.79	288	0.96	0.81–1.14	
			12.8–19.92 years	290	0.97	0.82–1.15		1316.79–2018.71	287	1.00	0.84–1.19	
			19.92–27.65 years	289	0.90	0.76–1.06		2018.71–2880	288	0.88	0.74–1.04	

Table 2 (continued)

Study, year, country	Study design (period)	Night work definition	Duration of non-day time work					Cumulative night shifts (intensity)				
			Exposure categories	No. of cases	RR[a]	95% CI	p-trend	Exposure categories	No. of cases	RR[a]	95% CI	p-trend
	have operated only day shift. JEM-based. No adjustment for confounders except age	rotations; never permanent night work	>27.67 years	287	0.88	0.74–1.05		>2880	289	0.89	0.75–1.07	
Wang et al., 2015, China	Case-control study from Guangzhou, China. Primary breast cancer diagnosed between 2010 and 2012. Cancer free controls were sampled from the same hospitals as cases. Information on exposure, was obtained by face-to-face interviews. 93% of cases and 96% of controls completed the question concerning night shift work	Night shift work is defined as working at least once per week for at least 6 months between midnight and 6 a.m.	All									
			Never	443	1	Reference						
			Ever	218	1.34	1.05–1.72						
			Premenopausal									
			Never	278	1	Reference						
			Ever	144	1.47	1.07–2.01						
			Postmenopausal									
			Never	162	1	Reference						
			Ever	72	1.17	0.77–1.80						

[a] Maximally adjusted

Typically, the main shift work related question is "How many years have you worked during the night?"

Many cohort studies [21, 22, 59, 61, 70••], even without information on night shift intensity, have shown increased breast cancer risk, however, only after long-term night work.

In contrast, a recent series of three large UK cohorts on night work and breast cancer found no association [62]. The main limitations in the UK cohorts are short follow-up time (3 years) and an aging survivor population (68 years old at baseline) where women may have stopped working years before start of follow-up and consequently may be negatively biased due to severe left-truncation [71–75]. Thus, it has recently been shown from the large American Nurses' Health Study (baseline 1988) that the risk of breast cancer attenuates and disappears years after cessation of night shifts. Thus, an estimated relative risk of 1.36 (95% CI, 1.07–1.78) among the nurses with at least 30 years rotation night work (mean age 60 years old at baseline) changed to a relative risk of 0.95 (95% CI, 0.77–1.17) when follow-up was continued from 1998 to 2012, thus including only nurses with post-retirement time [21, 70]. In contrast, the increased relative risk for nurses with at least 20 years of night shift work in the equivalent 19 years old younger cohort of Nurses' Health study II (41 years old at baseline in 1989) remained increased after the similar extended follow-up period (relative risk of 2.15 (95% C.I, 1.23–3.73)). Another recent study is based on payroll information from primary hospital employees in Denmark, where females are followed up for breast cancer during 2008–2012, i.e., for a maximum of 5 years [63]. There was no evidence of an association between cumulative night shift work and breast cancer risk in this study. In addition to the relatively short follow-up time, the major limitation of this study is lack of information on working time prior to 2007, because it is highly likely that the reference group of dayworkers in the period after 2007 have been exposed to night work at earlier ages before 2007 [76], since virtually all health professionals in Denmark have night work early in their career. Null results have also been found in one cohort with crude exposure assessment [60] based on Dutch Labor Force Surveys, which did not even have information on duration of night work [60]. Also a relative large cohort from Shanghai, China (mean age 53 years old at baseline in 1996–2000) reported null results [58], both based on applying a job exposure matrix at baseline and based on questionnaires on night work obtained during 2002–2004. Cohort members were followed up for breast cancer until the end of 2007, thus, only between 3 and maximum 7 years for the sub-cohort, including self-reported night work information, which limits the statistical power of the study, including only 73 women with night work and breast cancer. Further, it has been suggested that Asian ethnicity like the Chinese is less prone to circadian disturbance [77, 78]. Finally, in contrast, two independent cohorts from Sweden that included younger participants than the null studies and have longer follow-up time reported increased relative risks for long-term night shift workers [59, 61].

Case-Control Studies

As shown in Table 2, most case-control studies observe increased relative risks for breast cancer, though they are not all significantly increased [47, 49, 50, 52–54, 64–67, 79, 80].

A case-control study on nurses from Denmark attempted to differentiate between associations of breast cancer and evening shifts, rotating night shifts, and permanent night shifts, i.e., normal consecutive night work, respectively [80]. Results from this study indicates no association with breast cancer and evening shifts from 3 p.m. to 11 p.m. (OR = 0.9; 95% CI 0.4–1.9), but increased risk for both rotating (OR = 1.8; 1.2–2.8) and permanent night shifts from 11 p.m. to 7 p.m. (OR = 2.9; 95% CI 1.1–8.0). This was partly replicated in a study from Spain where the category of over 1800 permanent night shifts, indicated higher OR than the similar number of rotating night shifts, 1.48; 95% CI 0.81–2.68 versus OR = 1.08; 95% CI 0.66–1.79 [55].

It has been suggested that circadian disruption and misalignment of internal clocks normally occurs only after over three consecutive night shifts [26, 34]. Two case-control studies from Norway and Denmark have focused on the importance of number of consecutive night shifts and association with breast cancer risk in nurses and find only increased risk after at least 3–4 consecutive night shifts during at least 5 years [47, 50]. This was, however, not replicated in a more recent study from France [52].

The French study hypothesized that the risk of breast cancer should be more pronounced if night work starts before the first pregnancy, when mammary gland cells are incompletely differentiated than after first full-term pregnancy. Interestingly, the relative risk for these two situations were 1.47 (95% CI 1.02–2.12) and 1.09 (95% CI 0.77–1.55), respectively [52].

Subtypes of Breast Cancer

Despite the fact that breast cancer is a group of heterogeneous diseases, it has been treated as one entity in most, but not all studies on night work. This may also have contributed to the heterogeneity in results unless night work is associated with all subtypes, which is less likely. Different ages of study participant's that have different distributions of pre- and postmenopausal breast cancers have been suggested to have potential different etiology [81], thus may influence results on studies of night work and breast cancer. A recent study using pooled data from five case-control studies showed that it is in particular premenopausal breast cancer is increased after night work, rather than postmenopausal breast cancer [49, 52–54, 79, 82]. The same findings were seen in a recent study from China [56], and in the updated Nurse's Health studies [70••]. It can be generalized that this may further contribute to explain the heterogeneity in results of studies of night work and cancer where the age distribution and menopausal status is diverse. In particular, the recent negative UK cohorts consist in particular of women, who are almost all postmenopausal [62].

The distribution of different hormonal subtypes in breast cancer may also influence results [83, 84]. This has been studied in a number of case-control studies and in a case-control study nested within cohorts, where some heterogeneity in results has been observed [21, 53, 55, 56, 63, 85–87]. The most consistent findings is between night work and the human epidermal growth factor positive (HER2+) breast cancers [55, 56, 63, 86], which also has shown to be associated with melatonin suppression in experimental studies [88]. Thus, four such recent studies showed OR's in the range of 1.3–1.9, though results were only significant in one study from France [86].

Meta-analyses

Meta-analysis is a useful tool in order to make overall risk estimates of existing studies. A main requirement for conducting such analyses is, however, the existence of similar definitions of both exposure and outcome in included studies, which is not the case for any of the existing studies on night work and breast cancer [89]. Further, different criteria have been used for inclusion and exclusion of studies and each meta-analysis is thereby subject to different lists of studies. For instance, the most recent meta-analysis by Travis et al., which despite violation of normal criteria for conduction proper meta-analysis found no association when they included their own studies, was solely based on cohort studies [62], and did not include the most recent update of Nurses' Health studies [70••]. Overall, a number of recent meta-analyses have been published from authors without previous research within this field, and with somewhat different results and conclusions [62, 90–93].

General Limitations and Confounding

In industrialized societies, most people suffer from some circadian disruption originating from social obligations, so called social jet lag. Thus, most people normally delay bedtime and advance their wake up time, which is then often compensated during the days off [94]. In a population-based study in Germany, the average level of social jet lag was about 1.5 h [95]. This means that even a group of dayworkers is not fully appropriate as a "clean" reference group, which is ideally required in epidemiologic studies, which may dilute a true increased risk from night work, if such an association exists. In the majority of studies, adjustment for potential confounders seems without major influence. If any, the confounding seems mostly weakly negative (data not shown).

In general, the more recent case-control studies have a more detailed assessment of working time in comparison with both previous cases-control studies and most of the existing cohort studies. Almost all of the case-control studies were designed with the main purpose of investigating night work and breast cancer risk. Thus, most case-control studies have information on both duration of night work and intensity, e.g., number of lifetime shifts (Table 2). Furthermore, the case-control studies have normally obtained lifetime history of working time, job-by-job for a broad range of ages, whereas cohort studies often are prone to left-truncation bias because the age at baseline of disease-free cohort members is usually relatively high in order to capture as many cases in the near future. This is particularly problematic for studies of working time because complex mechanisms of selection in and out of night work exist, which may be better captured in case-control studies than in prospective cohort studies. On the other hand, case-control studies may be subject to recall and participation bias. Therefore, evidence based on results from different well-conducted study designs is also needed in the future.

New Study Directions

Animal models included in the IARC 2007 focused on the effect of ill-timed exposure to light and aspects of melatonin, including pinealectomy. Van Dycke et al. has recently reported on an animal model of rotating shift work where a group of control mice where one group of mice were exposed to 12 h of light and 12 h of darkness circles over about 70 weeks. Another group had the same cycle of exposure to light and darkness, but each week, the period of light and darkness was reversed. Almost all mice in both groups developed breast cancer. However, the group of mice that were exposed to simulated rotating night work had a significantly decreased latency of breast cancer of about 8 weeks compared to the control group [96•]. Timing and quality of meals in shift workers is significantly different from dayworkers, and breast cancer risk is a new avenue of research which should be included in future studies [97–99]. Moreover, some pioneering results concerning long-term night work and epigenetic changes should be explored further [16, 100].

Prevention

Although night work yet remains to be confirmed as a cause of breast cancer, initiatives for preventive actions may be prudent

[101]. In 2012, an international group suggested a few guidelines in order to prevent potential breast cancer after night work, especially by using only forward rotating shifts, limiting the period with night shift work and by limiting the number of consecutive night shifts [102]. In general, however, there is a lack of evidence-based studies on this topic, in particular concerning night work and potential health outcomes in general [103]. Thus, future in-depth understanding of mechanisms may improve evidence-based prevention [104].

Conclusion

The number of new studies on night work and breast cancer has increased over threefold during the last 10 years after the IARC evaluation in 2007. In general, the case-control studies are better in capturing at least some of the complexity of night shift work, including intensity of night work than the cohort studies. Further, all recent studies include information on most potential confounders for breast cancers, although confounding appears to be relatively low, and in most studies in a negative direction. Four recent cohort studies from the UK and Denmark, despite advances in relatively large study populations, have not provided evidence of an association between night work and breast cancer risk. These null findings may be due to limitations in the design of these studies. Overall, the observed heterogeneity in results from epidemiologic studies may at least partly be attributed to wide differences in the definitions of night work, study design, length of follow-up, left-truncation in cohort studies, lack of information on chronotype, social jet lag, and differences in the investigated populations' menopausal status and breast cancer subtypes. Future studies on night work and cancer should use standardized definition of working time, including information on number of consecutive shifts, diurnal preference, menopausal status, and meal intake patterns. Cohort studies should include lengthy follow-up of relative young people. Overall, evidence based on results from different well-conducted study designs is also needed in the future. Finally, there is a need for studies of sites of other cancers than breast cancer.

Overall, the epidemiological evidence of an association between shift work that includes night work has increased since the IARC evaluation in 2007, and it might soon be time for a reevaluation by IARC.

Compliance with Ethical Standards

Conflict of Interest Johnni Hansen declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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