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Review

Night shift work and breast cancer risk – 2023 update of epidemiologic evidence

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ABSTRACT

Introduction: Night shift work is a complex and frequent occupational exposure, and breast cancer stands as the most prevalent cancer in women. The International Agency for Research on Cancer (IARC) has twice classified night shift work as a probable breast carcinogen, with the latest classification in June 2019. Since that time, new epidemiologic data has emerged.

Methods: We searched PubMed for original articles based on cohort and case-control studies of "breast cancer and night shift work" published after the IARC evaluation in June 2019.

Results: In total six cohorts and four case-control studies were included in our review. Overall, we observed some support for associations between persistent (long duration or high frequency) night shift work and an increase in breast cancer risk, though most studies were relatively small and statistically under-powered. Moreover, the recent studies do not contribute further evidence regarding the interaction with menopausal status, diurnal preference, hormonal subtypes of breast cancer or gene-environment aspects, which were issues that were left from the IARC evaluation.

Conclusions: The available new results somewhat consolidate the epidemiological evidence from IARC's 2019 evaluation, and do not provide further evidence regarding interaction of interest, e.g. menopausal status, etc. Therefore, long term follow-up of prospective cohorts or nested case-control studies, including precise exposure assessment and examinations of relevant interactions such as menopausal status, diurnal preference, hormonal subtypes of breast cancer and gene-environment aspects, are warranted. Meanwhile, protective measures for the night workers should be considered.

1. Introduction

Working during the night, i.e. late evening and after midnight, has become a common occupational exposure, comprising about 10–20 % of the total workforce in Europe and the US.[1] In some countries, this proportion seems to be further increasing.[2]

Typically, individual night workers rotate between working day, evening, night and morning shift in myriads of different combinations. In contrast, permanent night work, i.e., where an individual regularly works all shifts at night, is very rare.[3,4] Typical sectors with night work include hospitals, police, firefighting, power stations and transportation, but also some industries where the production runs continuously for economic reasons.[1] Night work typically involves being awake during normal sleeping hours, obtaining fewer sleep hours during the day, experiencing sleep deprivation, mistimed eating patterns, and being exposed to artificial light during the normal dark period. Over longer periods, these factors may have a profound influence on human physiology and health, potentially including carcinogenic effects.[5-8]

The current major biological-based hypothesis for the link between night shift work and certain cancers involves disruption of the natural circadian rhythms.[9-15] The pioneering work in understanding the biology of circadian clocks and rhythms was in 2017 awarded with the Nobel prize.[16] Circadian rhythms are intrinsic, approximately 24 h periods, where primarily the eyes' recognition of the normal dark-light cycle maintain the synchrony with the Earth's natural 24-hours environment.[17] The central circadian pacemaker is located in the suprachiasmatic nuclei (SCN) of the hypothalamus, which is linked with photosensitive ganglion cells of the retina (eyes). SCN orchestrates peripheral clocks throughout the entire body, primarily via pineal gland secretion of the hormone melatonin into the blood, which normally peaks during the dark night.[18-20] Nightly exposure to light may disrupt normal biological timing at different organizational biological levels, ranging from molecular rhythms in individual cells to misalignment of behav-

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ioral cycles with environmental changes. This disruption may, in turn, influence biological processes related to cancer, such as cell proliferation, apoptosis and immune suppression.[14,21-24] Another partly related hypothesis suggests that light-at-night suppresses nocturnal melatonin levels, which diminish the oncostatic properties of this hormone.[15,25-28] This may lead to an increase in the circulating levels of estrogen, a key component in breast cancer development.[15,26,29-31]

Since the first relatively crude hypothesis testing epidemiological study on "non-day time work" and breast cancer was published over 20 years ago,[32] increasing research has elucidated links between night work and certain cancers, in particular breast cancer, the most frequent cancer in women in Western countries.[33]

In 2007, the International Agency for Research on Cancer (IARC) under World Health Organization (WHO) classified "shift work, which involves circadian disruption" as probably carcinogenic to humans (IARC group 2A). This classification was based on limited evidence for breast cancer in humans, suggesting a credible causal interpretation, but the possibility of chance, bias, and confounding could not be ruled out with reasonable confidence. Thus, only eight epidemiologic studies on night shift-work and breast cancer were available for the 2007 evaluation.[34] The strongest evidence came from two independent prospective cohort studies on nurses from the US, showing an increased breast cancer risk after 20–30 years of rotating night shift work.[35,36] Further, there was sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night).[34]

In 2019, with the availability of several new studies, IARC re-evaluated "night shift work", and once again classified this exposure as probably carcinogenic to humans.[1,37] The evidence for human breast cancer was limited this time because bias could not be reasonably ruled out. However, the IARC working group found that chance and confounding were not key issues at this time. The most consistent epidemiologic evidence for the association between night shift work and breast cancer came from case-control studies rather than cohort studies.[1,38] A pooled case-control study, based on five different studies conducted in Germany, Canada, Australia, France and Spain, with a harmonized exposure assessment and based on over 6000 breast cancer cases, was considered particularly informative by the IARC working group.[39] Unlike most other studies, the pooled study observed an increased risk for breast cancer primarily in premenopausal women rather than in postmenopausal women.[39] This finding was not fully supported by updated data from the Nurses Health studies, which are among the most influential cohorts.[40] It has been argued that the superior informativeness from case-control studies was due to more precise exposure assessments than in the cohort studies.[38] Thus, most case-control studies provided information on the intensity of night shift work, such as the number of night shifts during a week, month or year, instead of only duration (years) of night shift work without such qualifying information, which was the case in almost all cohort studies.

Furthermore, many cohort studies were limited by short follow-up time for cancer and lack of exposure history after baseline.[20] In addition, there was sufficient evidence in experimental animals for the carcinogenicity of alteration in the light–dark schedule.[1] Finally, the 2019 IARC working group found strong evidence in experimental systems where alteration in the light–dark schedule exhibited certain key characteristics of carcinogens, i.e., evidence of effects consistent with immunosuppression, chronic inflammation, and cell proliferation. The working group also considered hormonal subgroups of breast cancer, e.g., estrogen receptors, chronotype (morning or night preference), and gene-environment interactions, but did not find consistency in results and thus no noteworthy support for such potential modifiers.[1]

Parallelly with the latest IARC evaluation, the US National Toxicology Program (NTP) concluded in a comprehensive review based on epidemiologic studies, animal experiments and mechanistic studies, that there was high confidence that persistent night shift work that results in circadian disruption can cause breast cancer.[41]

The present review aims to give an overview of epidemiological studies on breast cancer incidence in women published after the IARC evaluation in 2019 and until the end of 2023, as well as identifying knowledge gaps, and give suggestions for future research.

2. Materials and methods

We searched PubMed for original articles on "breast cancer and night shift work" published after June 2019. Likewise in the recent IARC evaluation,[37] studies based on breast cancer mortality[42] or cross-sectional studies,[43] and night works assesses by use of Job Exposure Matrices were not considered.[42] Due to the relatively small number of available articles and the different definition of night work, results are not suitable as a basis for meta-analysis as recommended by the IARC working group.[1]

3. Results

Numerous small to middle-sized studies on night shift work have been published after the IARC evaluation in 2019. Results for cohorts, including one nested case-control study is shown in Table 1,[44-47] whereas Table 2 shows results for four case-control studies[48-53] of which one study has three publications.[50-52] Most studies used different definitions of night work. The number of breast cancer cases with night shift work ranged from 33 to 914 across these studies. All studies, except one,[49] provided information on duration of night shift work with a tendency of increasing risk by increasing duration. Only three studies provided information on intensity (night shifts per week, month or year) of night shift work.[48,52,53] Four studies stratified the results by menopausal status,[45,47,50,54] and three of the studies tended to observe the highest risk in post-menopausal women or women over 50 years old used as proxy 0.[47,50,55] Finally, only one study presented results based on the direction (forward and backward) of shifts and indicated, though based on few cases, a higher breast cancer risk of the more disruptive backward shifts compared with normal forward shifts,[50] which is in line with observations of highest sleep deprivation in that group.[55] One study provided results stratified by hormonal subtypes for breast cancer and did not show notable differences between subtypes, however, based on small numbers.[48] One study had information on diurnal preference (morning or evening chronotype) and did not report notable difference in risk.[46] Only a relatively few new studies have since the most recent IARC evaluation investigated gene-environment interactions in relation to night work. Overall, results from such studies are supportive of interactions with the network of metabolic changes, circadian regulation, including melatonin signaling and biosynthesis, sleep and sex hormone changes,[53,56–59] but still lack harmonization of methods and outcome as concluded from the IARC working group.[37]

4. Discussion

In total, results of ten epidemiological studies have been published after the most recent IARC evaluation from 2019, which comprised 26 epidemiologic studies of breast cancer. Thus, this is slightly more epidemiological studies than the eight studies totally available for the first IARC evaluation in 2007.[34] Overall, despite most studies are under powered, subsequent results somewhat support the association between persistent (long term of high intensity) night shift work and an increase in breast cancer risk, though no clear dose-response relations are provided. Thus, available new results present to some extent a consolidation rather than a significant improvement of the 2019 epidemiologic evidence. Further, the new studies do not contribute notable additional insights into the questions regarding interaction with menopausal status, diurnal preference, hormonal subtypes of breast cancer or gene-environment elements.

Harmonization of the definition of night work is important, as emphasized by an IARC working group on this specific topic just after

Table 1
Cohort studies on night work and breast cancer risk published after the IARC (Vol 124) evaluation in 2019.

Authors, year, country	Study design (period)	NSW definition	Night shift work metrics		
			Exposure categories	No. of cases	Relative risk (95 % CI), max. adjusted
Marina R. Sweeney et al., 2020, Canada	The Sister Study Cohort is a large cohort of women never diagnosed with breast cancer but who had a sister (full or half) diagnosed with breast cancer (2003–2009). Information on exposures. Exposure information was obtained from computer assisted telephone interview, home visit and self-administered questionnaire.	Worked at night (≥1 hour between 12:00–2:00 AM) in current job (baseline) and past jobs held ≥2 years	No NSW	2937	Reference
			Ever rotating NSW	160	1.08 (0.92–1.27)
			> 0–5 years	88	1.30 (1.05–1.61)
			> 5–10 years	30	0.81 (0.57–1.16)
			> 10 years	42	0.96 (0.71–1.31)
			Ever any NSW	1949	Reference
			> 0–5 years	914	1.12 (1.00–1.26)
			> 5–10 years	230	1.04 (0.90–1.19)
			> 10 years	350	0.92 (0.82–1.03)
			Premenopausal		
			Never rotating NSW	507	Reference
			Ever rotating NSW	23	0.92 (0.61–1.40)
			> 0–5 years	10	1.53 (0.97–2.42)
			> 5 years	< 5	ND
			Post menopausal		
			Never any NSW	2419	Reference
			Ever any NSW	134	1.09 (0.92–1.30)
			> 0–5 years	66	1.20 (0.94–1.53)
			> 5 years	68	1.01 (0.79–1.28)
Jessica McNeil et al., 2020, Canada	Alberta's Tomorrow Project Cohort (2004, 2008)	Years of work a schedule that included day or evening work that rotated with night work in the same month. NSW: Years working straight night work	Never straight night	324	Reference
			Ever straight night	42	0.88 (0.64–1.23)
			2 years latency adjustment		
			Never straight night	263	Reference
			Ever straight	34	0.87 (0.61–1.25)
			Never worked rotating shifts	258	Reference
			0.1–5.9 years	64	0.92 (0.70–1.21)
			≥ 6 years	45	1.02 (0.74–1.41)
			2 years latency adjustment		
			Never rotating shifts	213	Reference
			0.1–5.9 years rotating shifts	51	0.89 (0.65–1.21)
			≥ 6 years of rotating shifts	34	0.94 (0.65–1.86)

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Table 1 (*continued*)

Authors, year, country	Study design (period)	NSW definition	Night shift work metrics		
			Exposure categories	No. of cases	Relative risk (95 % CI), max. adjusted
Mikko Härma et al., 2022, Finland	Cohort study based on the Finnish Public Sector (FPS) study (2000–2016). Information on exposure obtained from self-administered questionnaires	Shift workers with night work (≥3 h between 22:00 and 06:00) and permanent night work.	Follow-up < 10 years		
			Day work	673	Reference
			Shift work with nights	128	1.19 (0.94–1.39)
			Follow-up ≥10 years		
			Day work	123	Reference
			Shift work with nights	34	1.22 (0.80–1.85)
			Follow-up < 10 years, < 50 years old		
			Day work	362	Reference
			Shift work with nights	81	1.26 (0.97–1.64)
			Follow-up ≥10 years, < 50 years old		
			Day work	83	Reference
			Shift work with nights	19	0.91 (0.53–1.56)
			Follow-up < 10 years, ≥ 50 years old		
			Day work	311	Reference
			Shift work with nights	47	1.17 (0.84–1.63)
			Follow-up ≥10 years, ≥ 50 years old		
			Day work	40	Reference
			Shift work with nights	15	2.05 (1.04–4.01)
			Hospital sub-cohort (n = 20,763)		
			Follow-up < 10 years		
			Day work always	10	Reference
			Shift work at night at baseline	30	1.36 (0.63–2.97)
			NSW 5–9 years	4	0.69 (0.20–2.41)
			NSW 10–14 years	7	1.48 (0.52–4.15)
			NSW 15+ years	19	1.65 (0.72–3.81)
			Follow-up ≥10 years		
			Day work always	25	Reference
			NSW at baseline	196	0.68 (0.41–1.12)
			NSW 5–9 years	8	0.37 (0.16–0.88)
			NSW 10–14 years	10	0.60 (0.31–1.17)
			NSW 15+ years	168	0.72 (0.44–1.19)

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Table 1 (*continued*)

Authors, year, country	Study design (period)	NSW definition	Night shift work metrics		
			Exposure categories	No. of cases	Relative risk (95 % CI), max. adjusted
Fei Chin Liu et al., 2022, Norway	Prospective case-cohort study within the Norwegian Offshore Petroleum Workers Cohort (1997–2017).	NSW: 14 consecutive days of night time work usually between 19:00 and 07:00.	Day work only	29	Reference
			Night/rollover shifts	20	1.06 (0.57–1.97)
	This study also provided results based on breast cancer subtypes, but based on very few cases (not shown).	Rollover: 7 consecutive days of day work (07:00 to 19:00) followed by 7 consecutive days of night time work usually between 19:00 and 07:00.	Night/rollover shifts < 1–6 years	6	0.72 (0.28–1.86)
			Night/rollover shifts ≥ 6 years	14	1.34 (0.67–2.72)
Eva Schernhammer et al., 2023, Finland	Prospective population based cohort of Finnish twins (1990–2018).	Self-reported (1990) based on current or latest work type. Rotating-shift work: rotating through morning, evening, of night shifts in either a two-shift or three-shift pattern	Day work only	325	Reference
			3-shifts or night only	49	1.58 (1.16–2.15)
			Morning chronotypes		
			Day work only	182	Reference
			3-shifts or night only	24	1.46 (0.93–2.28)
			Evening chronotypes		
			Day work only	140	Reference
			3-shifts or night only	22	1.56 (0.99–2.46)
Per Gustavsson et al.,2023, Sweden	Prospective cohort of health care workers based on registry data from Stockholm, excluding physicians (2008–2016)	NSW: ≥ 3 h between 22:00 and 06:00 h. Register based information on working time.	No night work	216	Reference
			Night work ever	83	0.96 (0.74–1.23)
			1–3 years night work	57	1.08 (0.80–1.44)
			4–7 years night work	21	0.65 (0.40–1.00)
			8+ years night work	5	2.80 (0.96–6.52)
			Premenopausal		
			Night work ever	108	Reference
			1–3 years night work	29	0.81 (0.52–1.20)
			4–7 years night work	10	0.57 (0.27–1.05)
			8+ years night work	0	(0.00–3.07)
			Postmenopausal		
			Night work ever	108	Reference
			1–3 years night work	28	1.59 (1.02–2.38)
			4–7 years night work	11	0.74 (0.37–1.33)
			8+ years night work	5	4.33 (1.45–10.57)

Abbreviation: NSW, night shift work.

Table 2
Case-control studies on night work and breast cancer risk published after the IARC (Vol 124) evaluation in 2019.

Study, year, country	Study design (period)	NSW definition	NSW metrics		
			Exposure categories	No. of cases	Relative risk (95 % CI), max. adjusted
Thu-Thi Pham et al., 2019, Korea	Case-control study from the Breast Cancer Center or Health Examination Center at the National Cancer Center. Information on exposures obtained through face-to-face interviews. (February 2012 to January 2018)	Ever having worked night shifts regularly between 9:00pm and 8:00am for at least 2 months lifetime	Never NSW	1539	Reference
			Ever	182	1.10 (0.89–1.40)
			Age at starting NSW		
			≤30 years	96	1.08 (0.80–1.49)
			>30 years	82	1.16 (0.83–1.63)
			Duration		
			≤10 years	145	1.05 (0.83–1.36)
			>10 years	35	1.44 (0.82–2.55)
			Number of days per week		
			1–5	88	1.13 (0.82–1.57)
			>5	78	1.16 (0.83–1.66)
			Lifetime cumulative frequency		
			≤10,000 h	94	1.08 (0.80–1.49)
			>10,000 to ≤35,000 h	63	1.09 (0.76–1.59)
			>35,000 h	23	1.30 (0.66–2.58)
			Pre-menopausal breast cancer		
			Never NSW	855	Reference
			Ever	99	1.18 (0.85–1.65)
			Duration		
			≤10 years	80	1.17 (0.81–1.68)
			>10 years	19	1.47 (0.67–3.25)
			Lifetime cumulative frequency		
			≤10,000 h	56	1.09 (0.71–1.66)
			>10,000 to ≤35,000 h	51	1.23 (0.70–2.17)
			>35,000 h	10	2.92 (0.78–10.76)
			Post-menopausal breast cancer		
			Never NSW	640	Reference
			Ever	81	1.16 (0.81–1.64)
			Duration		
			≤10 years	64	1.05 (0.71–1.53)
			>10 years	15	1.79 (0.72–4.47)
			Lifetime cumulative frequency		
			≤10,000 h	38	1.05 (0.65–1.71)
			>10,000 to ≤35,000 h	30	1.16 (0.67–2.02)
			>35,000 h	11	1.37 (0.50–3.73)
			Luminal A breast cancer		
			Never NSW	771	Reference
			Ever	89	1.09 (0.82–1.45)
			Age at starting NSW		
			≤30 years	50	1.16 (0.80–1.69)
			>30 years	38	1.08 (0.71–1.63)
			Duration		
			≤10 years	74	1.08 (0.80–1.47)
			>10 years	15	1.29 (0.64–2.61)
			Number of days per week		
			1–5	44	1.16 (0.78–1.72)
			>5	33	0.98 (0.63–1.54)
			Lifetime cumulative frequency		
			≤10,000 h	46	1.05 (0.72–1.54)
			>10,000 to ≤35,000 h	32	1.15 (0.73–1.81)
			>35,000 h	11	1.32 (0.57–3.03)
			Luminal B breast cancer		
			Never NSW	116	Reference
			Ever	18	1.36 (0.79–2.33)
			Age at starting NSW		
			≤30 years	5	0.81 (0.32–2.10)
			>30 years	12	1.86 (0.96–3.61)
			Duration		
			≤10 years	14	1.27 (0.70–2.30)
			>10 years	3	1.65 (0.45–5.98)
			Number of days per week		
			1–5	4	0.67 (0.24–1.91)
			>5	13	2.42 (1.25–4.69)
			Lifetime cumulative frequency		
			≤10,000 h	8	1.20 (0.56–2.58)
			>10,000 to ≤35,000 h	7	1.44 (0.63–3.31)
			>35,000 h	2	1.48 (0.31–7.05)
			HER2 breast cancer		
			Never NSW	169	Reference
			Ever	19	0.98 (0.58–1.16)

(*continued on next page*)

Table 2 (*continued*)

Study, year, country	Study design (period)	NSW definition	NSW metrics		
			Exposure categories	No. of cases	Relative risk (95 % CI), max. adjusted
			Age at starting NSW		
			≤30 years	9	0.96 (0.46–1.99)
			>30 years	9	1.00 (0.48–2.08)
			Duration		
			≤10 years	15	0.92 (0.52–1.63)
			>10 years	4	1.60 (0.52–4.96)
			Number of days per week		
			1–5	7	0.89 (0.39–2.00)
			>5	11	1.24 (0.62–2.48)
			Lifetime cumulative frequency		
			≤10,000 h	8	0.82 (0.38–1.76)
			>10,000 to ≤35,000 h	8	1.16 (0.53–2.54)
			>35,000 h	3	1.36 (0.37–4.98)
			Tripel-negative breast cancer		
			Never NSW	309	Reference
			Ever	39	1.10 (0.74–1.62)
			Age at starting NSW		
			≤30 years	19	0.93 (0.54–1.60)
			>30 years	19	1.36 (0.79–2.36)
			Duration		
			≤10 years	24	1.03 (0.67–1.59)
			>10 years	14	1.20 (0.54–1.91)
			Number of days per week		
			1–5	25	1.44 (0.87–2.36)
			>5	14	1.02 (0.54–1.91)
			Lifetime cumulative frequency		
			≤10,000 h	23	1.29 (0.78–2.12)
			> 10,000 to ≤ 35,000 h	9	0.68 (0.32–1.43)
			>35,000 h	6	1.42 (0.50–4.05)
Lilia Patricia Bustamante-Montes, 2019, Mexico	Case-control study from Instituto de Seguridad Social del Estado de México y Municipios Cancer Center. Information on exposures obtained by personal interview (Not available).	Working any of the hours from 9pm to 7am for at least one year.	No NSW	67	Reference
			Ever	33	8.58 (2.19–33.8)
Marta Szkiela et al., 2020, Poland (# Marta Szkiela et al., 2021, Poland (¤ Beata Świątkowska et al., 2023, Poland (!	Case-control study (2015–2019). Patients from patients of the Oncological Surgery Department and the Second Department of Oncological Surgery, Oncological Surgery Clinics of the Provincial Specialist Hospital M. Kopernik in Łód´z; the surgery department of Poddebice Health Center SP. Z O. O.; and the Provincial Specialist Hospital M. Skłodowska-Curie in Zgierz. The control group were patients of the Provincial Specialist Hospital Maria Skłodowska-Curie in Zgierz, and clients of the club FruFitness Zgierz and the Adrianna stable in Aleksandrów Łódzk. Information was obtained from an anonymous and voluntary self-administered questionnaire.	Ever having worked evening/night, rotating or other types of shifts.	Never NSW (#(¤(!	310	Reference
			Ever NSW (#	168	2.20 (1.57–3.08)
			Consecutive night shifts (¤		
			≤3	43	2.03* (1.23–2.10)
			>3	114	3.02* (3.34–4.34)
			Rotation (¤		
			Forward	148	2.58* (1.88–1.03)
			Backward	10	3.31* (3.52–0.64)
			NSW before illness (¤		
			≤10 years	8	1.06* (0.41–2.71)
			>10 years	154	2.91* (2.12–4.00)
			Duration of night work (¤		
			1–9 years	19	1.48* (0.76–2.89)
			10–19 years	74	3.16* (2.02–4.92)
			20–29 years	44	1.91* (1.68–5.04)
			30–39 years	27	2.55* (1.32–4.95)
			Post menopausal women (!		
			Never NSW	31	Reference
			Ever NSW	80	2.65 (1.34–5.22)
			<5 years NSW	30	2.11 (0.98–4.56)
			≥5 years NSW	25	3.43 (1.54–7.67)
			<6 times NSW / month	24	2.73 (1.15–6.52)
			≥6 times NSW / month	31	2.60 (1.24–5.46)
Song, 2023, China	Case-control study based on cases from Department of Surgery, Cancer Hospital, Chinese Academy of Medical Sciences. Controls were diagnosed with benign tumors at the same department and period (July 2011-December 2012)	Night work: Ever work between midnight and 5am for more than one year	Never night work	374	Reference
			Ever night work	104	0.84 (0.60–1.17)
			Duration: <10 years night work	48	0.75 (0.49–1.14)
			≥10 years night work	41	0.96 (0.60–1.56)
			Frequency: <10 times / month	52	0.81 (0.54–1.22)
			≥10 times / month	36	0.90 (0.55–1.48)

* Unadjusted.

Abbreviations: IARC, International Agency for Research on Cancer ; NSW, night shift work.

the first evaluation in 2007.[10] For example, when five individual case-control studies were pooled after the harmonization of night work definitions, there was a decline in the number of cases and controls,[39] but the results were more homogeneous than then when the results from each of the five studies were compared.[60-64] The IARC recommendation has only been partially followed in recent studies, which may, together with low statistical power, have contributed, at least partly, to the observed heterogeneity of results from these studies.

Positive association of night work and breast cancer have especially been observed in previous case-control studies recently evaluated by IARC.[1,38] A tendency of stronger associations in case-control studies than in cohort studies was also the case for the studies published after the IARC evaluation. A potential concern for past and recent case-control studies is the possibility of recall bias, i.e., breast cancer cases may recall night work differently than decease-free controls. A few studies have attempted to validate recall of night shift work in breast cancer studies. Härmä et al. compared self-reported working time with information from objective register data and found over 90 % sensitivity and specificity between self-reported shiftwork with night work.[65] Lizama et al. found that breast cancer patients more often than controls believed that shift work increased the risk of breast cancer, but this did no evaluation of resulting misclassification.[66] Finally, Vestergaard et al. compared data from a Danish questionnaire with objective payroll-data and found that female breast cancer patients had slightly better recall of previous night shift work than controls. They observed that both breast cancer patients and controls recalled previous non-night work with low specificity.[67] If this can be generalized to other case-control studies of breast cancer and working time studies, this may result in a small overestimation of the relative breast cancer risk. Therefore, a risk of bias assessment shall be addressed in future retrospective assessment of night work in future studies, as suggested by e.g. Morgan et al.,[68] and a recent IARC working group addressing the specific topic of night shift work.[69] Studies that accumulate information on objective exact working time based on payroll data from public health care employees in e.g. Danmark,[70] Finland[71] and Sweden,[47] as well as the American Manufacture Cohort,[72,73] may be valuable for epidemiologic research of chronic diseases like cancer, when they in the future will capture near lifelong work history and sufficient follow-up time for chronic diseases. Furthermore, prospective cohorts specifically designed for investing outcomes from night work, including detailed information on potential confounders, including e.g. reproductive factors, use of contraceptives, hormone replacement therapy may contribute significantly to the evidence. New avenues in night work and cancer research are meal timing and sleep habits, which may also qualify future studies.[74-77] A prominent example of a new cohort with detailed exposure information is the ongoing Dutch Nightingale study,[78] which still needs further years of follow-up for breast cancer in order to provide meaningful epidemiological results.

Hispanic, Black and low-paid workers seem underrepresented in existing studies of night work and cancer.[72] Focus on such groups should therefore be prioritized in future studies. Mistimed eating patterns, sleep deprivation and lack of sleep regularity are common effects of night-work and influence on the breast cancer risk needs further investigations.[74,79-82] Additionally, more studies focusing on different mechanistic aspects of night work, such as changes in melatonin and steroid production, metabolic profiling, and cellular immune responses may help our future understanding.[58,59,83] Further, there is a need for intervention studies to address short and long term physiological consequences of night work compared to day work.[84] Finally, no studies have so far addressed the issue that the increasing survival of breast cancer results in a higher proportion of patients that return to work, including night work, after treatment. Thus, it is currently unknow if these women will face an additional subsequent risk of cancer.[85]

It has been estimated that 5–7 % of all breast cancer may be attributed to night shift work,[2,86,87] assuming night work causes this disease. Since night work is necessary in many sectors in modern society, detailed insight into eventual low or no-effect levels of night work are needed. For example, a study of Danish nurses that worked only 1–2 night shifts per week, regardless of the duration in years with night shifts, indicated that they posed the same breast cancer risk as nurses who had never worked night shifts.[88] Additionally, a study of Norwegian nurses indicated increasing breast cancer by increasing number of working consecutive nights.[89] Thus, similar studies are warranted in order to validate or refute results from these two Scandinavian studies. While awaiting more precise results to reduce potential health risks, recommendations on night shift schedules should be implemented, as recently suggested.[90,91]

In conclusion, this review of all studies of night work and breast cancer incidence published after the IARC 2019 evaluation, present a weak consolidation of evidence, but without strong further clarification of the 2019 IARC evaluation of limited epidemiologic evidence. Night shift work is the most frequent occupational exposure with the potential to impact female breast cancer. Therefore, large, high-quality prospective cohorts with long duration of follow-up for breast cancer, including detailed assessment of working time for diverse types of workers and races, meal timing, sleep habits and different breast cancer subtypes, are still warranted to assess the extent of breast cancer carcinogenicity. Cohort studies may be replaced by well conducted case-control studies in order to speed-up the hunt for evidence.[38] Studies of survival of breast cancer cases with and without subsequent night work are also needed. Meanwhile, there is sufficient evidence for pursuing preventive initiatives for night workers, which may also reduce the risks for other health outcomes.[90,91]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

J.H. concepted and wrote the first draft of the manuscript. Together with J.E.P. he interpreted the data and wrote the final version. Both authors approved the final version of the manuscript.

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