Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history

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Abstract

Night shift work has been suspected to increase breast cancer risk but epidemiological studies have been inconsistent due to heterogeneous assessment of exposure to night work. To overcome this limitation, we pooled data of five population-based case–control studies from Australia, Canada, France, Germany, and Spain into a single harmonized dataset using a common definition of night work including 6093 breast cancer cases and 6933 population controls.

The odds ratio for breast cancer in women who ever worked at night for at least three hours between midnight and 5 a.m. as compared to never night workers was 1.12 (95% CI 1.00-1.25). Among pre-menopausal women, this odds ratio was 1.26 [1.06-1.51], increasing to 1.36 [1.07-1.74] for night shifts ≥10 hours, 1.80 [1.20-2.71] for work ≥ 3 nights/week, and 2.55 [1.03-6.30] for both duration of night work ≥10 years and exposure intensity ≥ 3 nights/week. Breast cancer risk in pre-menopausal women was higher in current or recent night workers (OR=1.41 [1.06-1.88]) than in those who had stopped night work more than 2 years ago. Breast cancer in post-menopausal women was not associated with night work whatever the exposure metric. The increase in risk was restricted to ER+ tumors, particularly those who were both ER+ and HER2 +.

These results support the hypothesis that night shift work increases the risk of breast cancer in pre-menopausal women, particularly those with high intensity and long duration of exposure. Risk difference between pre- and post-menopausal women deserves further scrutiny.

Key words: Night shift work, Breast Cancer, pooled analysis, case-control study, circadian disruption

Introduction

Shift work involving circadian disruption was classified as a probable carcinogen (group 2A) by IARC in 2007 based on sufficient evidence in experimental animals and limited evidence in humans [1]. The animal studies showed that variations in circadian rhythm induced by various methods of manipulating the light/dark cycle had an impact on tumor development, and several biological mechanisms could explain how the 'disruption of circadian rhythm' may promote carcinogenesis [2]. The epidemiological studies evaluated in the IARC report mainly addressed breast cancer risk, and found only modest increases in risk, in particular in nurses who had worked at night for 20 years or more [3].

Since the publication of this report, results of additional epidemiological studies on breast cancer in relation to night shift work have been inconsistent [4-17]. Differing characterizations of exposure to night work have been used in these studies in terms of intensity, length of night shifts, number of consecutive nights, and rotation patterns, and not all studies have assessed exposure over the full occupational history (e.g.[13, 15, 18]).

In addition, cohort studies conducted in occupational groups with a specific work time pattern (e.g. nurses) limit extrapolation to other groups with different schedules. Meta-analyses of case-control and cohort studies have reported increases of about 20% in summary relative risks of breast cancer in women who worked at night [19-22], while a recent meta-analysis of prospective cohort studies did not find any increased risk of breast cancer in women who ever worked at night, or in those who had long duration of exposure to night work [17]. These meta-analyses aggregated findings from studies that used heterogeneous definitions of night work and different exposure metrics, making their combined interpretation difficult.

In the present paper, we conducted a pooled analysis of individual level, rather than aggregated, data from studies of night work and breast cancer by recoding night work to allow a common characterization of exposure across studies. To this end, we followed, the recommendations made by an IARC expert panel [23] for characterizing exposure to night work that impacts on the circadian rhythm. We also focused on general population studies with complete work history to investigate the role of temporal pattern of exposure.

Material and methods

Study selection

We identified 30 publications on night work and breast cancer from a literature search in mid-2016 and excluded six meta-analysis articles that did not provide original data. From the remaining 24 original epidemiological studies, only those with detailed information on work history and work time schedules were considered for inclusion in the pooled analysis. We also sought to include general population studies not restricted to a single occupation to capture a wide range of work time schedules.

We finally retained five recent population-based case-control studies from Australia (BCEES) [9], Canada (CBCS) [7], France (CECILE) [8], Germany (GENICA) [4], and Spain (MCC-Spain) [11] (Table 1). Study investigators provided the original de-identified data for the study participants. The coordinating center was responsible for constituting and maintaining the pooled dataset, i.e. performing quality controls, recoding work time schedules using a common definition of night work, harmonizing data on breast cancer risk factors, and conducting the statistical analyses.

Selection of study subjects and methods of data collection in the original studies

Details on study design and night work exposure assessment in each study are given in the original papers [8, 7, 4, 11, 9]. Briefly, the cases were histologically confirmed breast cancer patients recruited from major hospitals in the study areas (France, Canada, Germany, Spain) or from the regional cancer registry (Canada, Australia). The periods of cancer incidence ranged from 2000-2004 at the earliest in Germany to 2008-2013 at the most recent in Spain.

Controls were women with no previous history of breast cancer and were frequency-matched by age to the cases. They were recruited from the same source population as the cases using the telephone directory (France), the electoral roll (Australia), rosters of general practitioners (Spain), population registry (Germany), or among women attending the regional population screening mammography program (Canada). In total, 6093 breast cancer cases and 6933 controls were included in the pooled analysis, representing a total of more than 54,000 job periods. The definitions of night work in the original publications

differed widely between studies, as can be seen in Table 1. According to these definitions, the proportion of night workers ranged from 7.0% in Germany to 34.4% in Canada.

Assessment of exposure to night work in each study and in the pooled analysis

Information on work time schedules in the original datasets was obtained for each job held for more than six months (twelve months in Spain) in a woman's work history. These questionnaires were administered during in-person interviews in France and Spain. In Canada the questionnaire was either self-administered or administered by phone, depending on the subject preference. In Australia and Germany, women were first asked during an in-person interview (Germany) or self-administered questionnaire (Australia) if they ever worked night shifts, and those women were re-contacted by phone to complete an interview on details of work time schedules.

Data provided by investigators included the year when each job started and ended, the number of working hours per week, and a code for job title. Hours at start and end of work were available for all jobs in the Canadian and Spanish studies, jobs that included at least one working hour between 11 p.m. and 5 a.m. in the French study, jobs that involved "shift work" in the German study, and jobs that included any number of hours between midnight and 5a.m. in the Australian study (Table 1). The number of nights per week in the French, German and Spanish studies was directly obtained from the questionnaire ("how many nights per week or month did you have on average while you were employed in that job?"); in Canada, women were asked to report the "percentage of time worked at each of day, evening or night shifts"; for this study, the number of nights per week was estimated using the formula: (number of work hours per week) x (percent of working time at night) / (length of night shift in hours). No data on the frequency of night shifts was available in the Australian study, which was therefore excluded from the analyses where this variable was used.

In the combined dataset, any job that included three or more working hours between midnight and 5 a.m. was classified as a job involving night work [23]. Based on this definition, we used the following exposure metrics for characterizing a woman's lifetime exposure to night work: duration (i.e. total number of years in jobs involving night work); length of night shifts (mean number of hours between start and end of shift, averaged over the duration of all jobs involving night work); intensity (mean number of night shifts

per week averaged over the duration of all jobs involving night work (not available for Australia)); and time since last night shift (years between last night shift and date of diagnosis for the cases or date of recruitment for the controls). We also calculated the cumulative number of night shifts during lifetime (intensity x duration) and the average number of night hours per week (intensity x night shift length).

Breast cancer risk factors

Data on socio-demographic, reproductive, hormonal, anthropometric characteristics, and lifestyle habits associated with breast cancer (age, age at menarche, age at first full-term pregnancy, parity, duration of breastfeeding, use of menopausal hormone therapy and oral contraceptives, family history of breast cancer in first-degree relatives, alcohol consumption, tobacco smoking, body mass index (BMI) measured from 1 to 2 years before diagnosis depending on the study, and menopausal status) were obtained for each participant. All variables were recoded into identical categories and compiled into a combined dataset.

Statistical Analyses

Odds ratios and 95% confidence limits for the association between night work exposure metrics and breast cancer were calculated using conditional logistic regression models stratified by 5-year age group and study. The following categories were used for duration of night work (<10, 10-19, ≥ 20 years), length of night shifts (<8, 8-9, ≥10 hours), intensity (<1, 1-2, ≥3 nights per week), time since last night shift (0-2, 3-9, 10-19, ≥20 years), cumulative number of night shifts over the working lifetime (<300, 300-999, ≥1000) and average number of night hours per week (<11, 11-19, ≥20 hours). Analyses were conducted for all women combined, and for pre- and post-menopausal women separately using women who had never worked at night as the reference exposure group. Women were considered menopausal if at the time of cancer diagnosis (for cases) or study recruitment (for controls) they had not menstruated for twelve or more months, if they had had bilateral oophorectomy, or if they had used menopausal hormone therapy before cessation of menstruation. Analyses were adjusted for age at menarche (<12, 12, 13, ≥14), age at first full-term pregnancy (<22, 22–24, 25–27, ≥28 years), parity (nulliparous, 1, 2, 3, ≥4 children), summed duration of breastfeeding (never, <6 months, 6-11 months, ≥12 months), use of menopausal hormone therapy (yes, no), use of oral

contraceptive (yes, no), family history of breast cancer in first-degree relatives (yes, no), current alcohol drinking (yes, no), ever tobacco smoking (yes, no), and body mass index (BMI) (<18.5, 18.5–24, 25–29, ≥30 kg/m^2). To test exposure-response trends, we fitted models where duration of night work, frequency of night shift, and length of night shift were introduced as continuous variables in the model, assuming a linear relationship with breast cancer risk. Differences in the effect of shift work by menopausal status were examined by adding the appropriate interaction terms into the model. Heterogeneity between studies was tested using the Cochran's Q test and I^2 statistic [24].

Analyses were repeated for breast cancer subtypes defined by hormone receptor status (estrogen receptor ER and human epidermal growth factor receptor HER2). Because PR status was not available in all studies, and because most PR-positive tumors were ER-positive, results including PR status were not informative and are not shown.

Sensitivity analyses were also conducted using alternative definitions of night work, i.e. jobs involving one or more working hour or jobs involving five hours (instead of ≥3 hours) between midnight and 5 a.m. All statistical analyses were conducted using SAS software version 9.4.

Results

The pooled dataset of all five studies with information on night work included 6093 cases and 6933 controls. The subset of the four studies where the number of nights per week was available (i.e. excluding Australia) comprised 4894 cases and 5154 controls. Selected characteristics of the study populations are shown in supplemental Table S1. Mean age varied between 54.7 years in France to 58.7 years in Spain. The proportion of pre-menopausal women was below 25% in Australia and Germany, 30% in Spain and 38% in France and Canada. The prevalence of obesity (BMI ≥30 kg/m2) ranged from 12% to 23%. Nulliparous women were 7% in France and 29% in Canada. Parity, age at FFTP, breastfeeding, use of oral contraceptives or menopausal hormone therapy differed widely between countries.

Using a common definition of night work across all studies (i.e. classifying as ever night worker any woman with work shifts of at least three hours between midnight and 5 a.m. in any job), the proportion of ever night workers among controls was around 17% in the Australian and Canadian studies, 9% in France and Spain, and 6% in Germany

(Table 1). These proportions were lower than the values in the original publications due to more stringent definition of night work in this pooled analysis (Table 1).

The pooled odds ratio for breast cancer in women who ever worked at night was 1.12 (95% CI 1.00-1.25), ranging from 1.00 in Canada and Germany to 1.27 in Australia (Table 2). No heterogeneity between studies was detected (Q test p=0.44, I^2=0%). The pooled OR was 1.26 (95%CI 1.06-1.51) in pre-menopausal and 1.04 (95%CI 0.90-1.19) in post-menopausal women (p for interaction = 0.16). The ORs were higher in pre- than in post-menopausal women in all studies, with the exception of the German study, which had small numbers. Tests of heterogeneity between studies did not reach statistical significance in either pre- (Q test p=0.62, I^2=0%) or post- (Q test p=0.21, I^2=31%) menopausal women.

The ORs for breast cancer associated with night work exposure metrics are shown in Table 3. In pre- and post-menopausal women combined, breast cancer risk did not increase with lifetime duration of night work (p-trend=0.45) or with length of night shifts (p-trend=0.38). Breast cancer risk in women who were currently working at night or who had recently quit night work (≤ 2 years) (OR=1.26; 95% CI 1.02-1.55), was higher than that of women who had stopped working at night more than two years ago. Based on the four studies that provided data on night work intensity (i.e. number of nights per week), the OR for breast cancer was 1.26 (95% CI 0.97-1.63) for women who worked three or more nights per week and 1.28 (95%CI 1.01-1.60) for women who worked at night for 20 or more hours per week (intensity x length of shifts). No clear increase in risk was seen with lifetime cumulative number of night shifts (p-trend=0.10).

Table 3 also shows that the associations between night work exposure metrics and breast cancer were restricted to pre-menopausal women. Among these women, elevated odds ratios were seen for length of night shifts ≥ 10 hours (OR=1.36; 95%CI 1.07-1.74) and time since last night shift ≤ 2 years (OR=1.41; 95%CI 1.06-1.88). Restricting the analysis to four studies with data on exposure intensity, elevated odds ratios were apparent for premenopausal women who worked three or more nights per week (OR=1.80; 95%CI 1.20-2.71), and those who worked 20 or more night hours per week (OR=1.57; 95%CI 1.11-2.23). All ORs were close to one among post-menopausal women.

The pooled odds ratios for all exposure metrics based on the four studies with exposure intensity are shown in Supplemental Table S2. In this table, the OR for breast cancer associated with exposure duration ≥20 years reached 1.68 (95% CI 0.98-2.83), but no major change was observed for length of night shifts and for time since last night shift. The results for night work exposure metrics tabulated for each study separately are shown in Supplemental table S3. No heterogeneity between studies was detected.

We also explored the effect of exposure intensity ≥3 nights per week, stratified on lifetime exposure duration (< 10 or ≥10 years), length of night shifts (<10 or ≥10 hours) and time since last night shift (≤2 or >2 years) based on the four studies with information on exposure intensity (Table 4). Among pre-menopausal women, the ORs associated with ≥ 3 nights per week were higher in categories with longer exposure duration (≥ 10 years: OR=2.55 95% CI 1.03-6.30 for), longer night shifts (≥ 10 hours/shift: OR=2.15; 95%CI 1.21-3.84), and in more recent night workers (last night work ≤ 2 years: OR=2.76; 95% CI 1.38-5.53). High exposure intensity ≥ 3 nights per week was not associated with post-menopausal breast cancer regardless of duration of exposure to night work, or length of night shift. Of note, the odds ratio associated with high exposure intensity and time since last night work ≤ 2 years was increased by 58% in postmenopausal women, although the increase was not statistically significant possibly because of small numbers.

Table 5 shows ORs associated with ever night work for breast cancer subtypes defined by hormone receptor status. Information on the ER status and HER2 status was missing in 76 and 181 cases, respectively. An elevated OR was seen for ER-positive tumors (OR=1.19; 95%CI 1.06-1.33) among all participants, but the elevation in risk was restricted to pre-menopausal women (OR=1.36; 95%CI 1.12-1.64). When ER-positive tumors were further subdivided into HER2-positive and HER2-negative tumors, elevated ORs were observed for the ER+/HER2+ tumor subtype in both pre- and in post-menopausal women (OR=1.77; 95%CI 1.16-2.70; and, OR=1.59; 95% CI 1.11-2.28, respectively). Exposure to night work was not associated with the ER-negative breast cancer subtype.

Finally, we also performed sensitivity analyses using varying definitions of night work, i.e. ≥ 1 hour or 5 hours between midnight and 5 a.m., and results changed only slightly (Supplemental Table S4).

Discussion

The major strengths of this pooled analysis are its large sample size including a large number of premenopausal women, detailed information of work time schedules over the entire work history, and use of a common definition of night work that led to a harmonized dataset with population-based individual-level information. When compared to never night workers, we found that the incidence of breast cancer for women who ever worked at night increased by 12%. This increase was stronger among premenopausal women, particularly those with ≥3 nights per week intensity of exposure. In contrast, no association between night work and breast cancer was detected among post-menopausal women when tumour type was not considered. The association of night work with breast cancer was restricted to the ER+ tumors subtypes, particularly those that were both ER+ and HER2+, for both pre- and post-menopausal women.

Despite convincing evidence from experimental animal studies supporting a link between circadian disruption and cancer [1], results of epidemiological studies published to date have been inconsistent, with some studies [6, 25, 5, 13, 16, 10], but not all [17, 14, 12], reporting an association between night work and breast cancer. Variations in the definitions of night work and variations in exposure assessment methods can be a source of inconsistency between study findings. Some studies used job-exposure matrices to assess exposure to night work based on the women's occupational title and industry [26, 27, 12] which may lead to misclassification errors; other studies analyzed the duration of night work [28, 3, 29, 16] without consideration of other surrogate measures of circadian disruption such as intensity of night work, length of night shifts, or frequency of rotations in shifts [23]. Moreover, incomplete assessment of exposure in previous studies has prevented the examination of specific exposure windows during a lifetime [17]. In addition to these limitations, the results of several cohort studies that focused on one particular occupational group (e.g. nurses [3, 30], military [6], textile workers [14], and radio and telegraph operators [31]) may not be applicable to other groups with different patterns of work time schedules.

Meta-analyses based on aggregated data of case-control and cohort studies have reported increased meta-RRs of breast cancer ranging from 10-20% for night work or shift work, depending on the studies included [19-22, 14]. However, heterogeneity between studies was observed, with higher meta-RRs for case-control than for cohort

studies [19]. In another recent meta-analysis restricted to large prospective cohort studies, and including mainly post-menopausal women, the meta-RR for breast cancer was not increased, and no association with duration of night shift work was observed [17]. Because the definition of night work and the methods of exposure assessment have been different across studies, meta-analyses based on aggregated data are difficult to interpret.

To overcome these limitations, we re-coded exposure to night work of each participant in five epidemiological studies. The definition of at least three working hours between midnight and 5 a.m. recommended by an IARC expert panel [23] was used to calculate several night work exposure metrics. We found that night work characteristics indicative of high exposure intensity (3 or more nights per week) and long night shifts (10 or more hours) were associated with an increased risk of breast cancer in premenopausal women. This is a novel finding indicating that an elevated number of nights worked per week and long working hours at night may induce stronger disruption of circadian rhythm [23], one of the mechanisms by which night work may increase the risk of cancer [2]. Our data also suggested that long duration of night work over lifetime (≥10 years) combined with high intensity (average of 3 or more nights per week) was associated with increased breast cancer risk in pre-menopausal women. Taken together, our findings were consistent with the Nurses' Health Study II showing that nurses who worked rotating night shifts for at least 3 nights per month for 20 or more years, particularly during young adulthood, were at increased risk of breast cancer [32]. Several studies [28, 3, 16, 30, 25] also reported increased risks of breast cancer associated with long duration of exposure.

Our data also suggested a greater increase in risk among women currently or recently (≤ 2 years) working night shifts, than in those who had stopped working night shifts more than 2 years ago. This temporal pattern may explain at least partly the risk difference between pre- and postmenopausal women, as the latters include a large proportion of women who have stopped working at night for a long period of time. We also observed (Table 4) that the few postmenopausal women who did not stop working at night in the last 2 years and who had worked for ≥ 3 nights/week had an increased risk of breast cancer, although the increase was not statistically significant.

In line with our observation, it has already been suggested that the null results observed in the meta-analysis of prospective cohort studies by Travis et al. [17] may be

explained by the older age of the women included in these studies, reflecting exposure to night work that occurred a considerable time in the past [33]. Other explanations for discrepant findings between pre- and post-menopausal women include higher exposure intensity in the younger generations of women due to rapid expansion of night work during the last few decades, or perhaps night work exposures in early adulthood impacting risk more due to an increased susceptibility of breast tissue to circadian disruption in earlier life stages. Divergent findings may also be explained by interactions with risk factors for breast cancer that behave differently between pre- and post-menopausal women (e.g. BMI) or with lifestyle or reproductive factors that are distributed differently for younger and older women (e.g. alcohol, smoking, parity).

In the analysis by breast cancer subtype defined by hormone receptor status, we found that the association between pre-menopausal breast cancer and night work was stronger in ER-positive tumors, pointing to a possible role of estrogens in a pathway between night work and breast cancer. Among ER-positive tumors, we also found that night work was more strongly associated with risk of the breast cancer subtype defined by both ER-positive and HER2-positive receptor status, for both pre- and post-menopausal women. The reason for such an association is unclear and requires confirmation, and exploration, by additional studies.

This pooled analysis has several limitations. First, all studies were retrospective in design. However, potential recall bias was minimized by the use of standardized questionnaires to obtain information on working time schedule for each job over a lifetime, without specific focus on night work. Despite the use of a common framework across the five studies for assessing exposure to night work, complete standardization of exposure metrics may not have been achieved because of the different approaches used in each study to obtain information on night work. This may have led to misclassification errors across exposure categories. Finally, we could not investigate all domains that may be important to circadian disruption resulting from night shift work [23], such as information on the type of night work (rotating vs. permanent, speed and direction of rotation), number of consecutive night shifts, or data on sleep habits, exposure to ambient light at night, or chronotype.

Conversely, strengths of this study include the unique dataset compiled from individual data with common assessment of key exposure characteristics, the detailed

exposure information including shift work intensity and length, the large sample size, particularly of premenopausal women, allowing good statistical power and adjustment for confounders. Sensitivity analyses using various definitions of night work and various cut-offs of quantitative variables were consistent with the main analysis.

Overall, our study captured important characteristics of night work among many different patterns of shiftwork, and analyzed characteristics that can significantly disrupt the circadian clock [23, 34]. Intensity of night work, measured as the number of nights per week, was most strongly associated with breast cancer risk among younger women. Our data also suggest that length of night shifts and lifetime duration of night work are important parameters of exposure related to risk, that the risk may decrease after cessation of exposure, and that the risk to specific sub-types of breast cancer (ER-positive tumors) may be affected greater.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

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Table 1: Description of the studies included in the pooled analysis of Night Work and Breast Cancer

Study	Period	Age range	Cases n	Cases Source	Controls n	Controls Source	Data Collection	Original studies — Definition of night work	Original studies — Proportion of night workers in controls	Pooled analysis — Proportion of night workers in controls[a]
Australia Fritschi, 2013	2009 2011	18-80	1199	Cancer Registry of Western Australia	1779	Electoral roll	Self-administered questionnaire and phone interview	Work between midnight and 5 am	21.3%	17.2%
Canada Grundy, 2013	2005 2010	40-80	1001 129	British Columbia Cancer Registry Hotel Dieu Breast Assessment Program	1014 155	B C Screening Mammography Program Hotel Dieu Breast Assessment Program	Phone interview or self-administered questionnaire	≥50% of work time spent on evening or night shifts	34.4%	16.7%
France Menegaux, 2013	2005 2007	25-75	1230	Hospitals and Cancer Registry of 2 areas	1316	Phone directory	Face-to-face interview	≥ 1h between 11 pm and 5am	11.2%	8.5%
Germany Pesch, 2010	2000 2004	<80	840	14 hospitals of Region of Bonn	881	Population registry	Face-to-face and phone interview	5 hours between midnight and 5am in shift workers	7.0%	6.0%
Spain Papantoniou, 2015	2008 2013	20-85	1694	Hospitals in 10 regions	1788	Rosters of general practitioners	Face-to-face interview	Work between midnight and 6 am	13.3%	8.7%
ALL			6093		6933					

[a] Night worker: any job during work history involving 3 or more working hours between midnight and 5 am

Table 2: Odds ratios for breast cancer in ever night workers, stratified by study and menopausal status

Night work	All women				Premenopausal women				Postmenopausal women			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[b]	95% CI	Cases	Controls	OR[c]	95% CI
Australia												
Never	949	1473	1	ref	276	332	1	ref	673	1141	1	ref
Ever	250	306	1.27	[1.05-1.54]	79	73	1.48	[1.02-2.15]	171	233	1.24	[0.99-1.55]
Canada												
Never	947	968	1	ref	290	367	1	ref	657	601	1	ref
Ever	183	201	1.00	[0.79-1.25]	76	78	1.45	[1.00-2.11]	107	123	0.81	[0.60-1.08]
France												
Never	1111	1204	1	ref	424	445	1	ref	687	759	1	ref
Ever	119	112	1.21	[0.91-1.61]	69	55	1.42	[0.95-2.12]	50	57	0.98	[0.65-1.49]
Germany												
Never	789	829	1	ref	161	159	1	ref	628	670	1	ref
Ever	51	52	1.00	[0.66-1.51]	16	17	0.76	[0.35-1.68]	35	35	1.06	[0.64-1.73]
Spain												
Never	1526	1633	1	ref	518	466	1	ref	1007	1166	1	ref
Ever	168	155	1.12	[0.88-1.42]	84	67	1.22	[0.85-1.75]	84	88	1.03	[0.74-1.42]
All studies[d]												
Never	5322	6107	1	ref	1669	1769	1	ref	3652	4337	1	ref
Ever	771	826	1.12	[1.00-1.25]	324	290	1.26	[1.06-1.51]	447	536	1.04	[0.90-1.19]

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[a] Odds ratios calculated using conditional logistic regression models stratified by age group (5-year) and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, body mass index, alcohol, tobacco, menopausal hormone therapy, and menopausal status

[b] Odds ratios calculated using conditional logistic regression models stratified by age group (5-year) and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, body mass index, alcohol, and tobacco smoking.

[c] Odds ratios calculated using conditional logistic regression models stratified by age group (5-year) and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, BMI, alcohol, tobacco, and menopausal hormone therapy

[d] Conditional logistic regression models further stratified by study

Table 3: Odds ratios for breast cancer associated with metrics of night work exposure in the pooled analysis. Exposure metrics requiring information on night work intensity were available only in four studies (Canada, France, Germany and Spain).

	All women				Premenopausal women				Postmenopausal women			
	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI	Cases	Controls	OR[a]	95% CI
Duration (years) (b)												
Never worked at night	5322	6107	1	ref	1669	1769	1	ref	3652	4337	1	ref
<10 years	461	474	1.18	[1.03-1.36]	210	179	1.33	[1.07-1.65]	251	295	1.09	[0.91-1.31]
10-19 years	154	186	0.98	[0.78-1.22]	69	74	1.05	[0.74-1.47]	85	112	0.92	[0.68-1.23]
≥20 years	151	161	1.10	[0.87-1.39]	42	36	1.34	[0.85-2.13]	109	125	1.04	[0.80-1.36]
Length of night shifts (hours) (b)												
Never worked at night	5322	6107	1	ref	1669	1769	1	ref	3652	4337	1	ref
<8 hours	84	91	1.06	[0.78-1.43]	37	40	1.03	[0.65-1.64]	47	51	1.09	[0.73-1.65]
8-9 hours	324	349	1.15	[0.98-1.34]	111	108	1.20	[0.91-1.60]	213	241	1.12	[0.92-1.36]
≥10 hours	344	366	1.12	[0.96-1.31]	167	136	1.36	[1.07-1.74]	177	230	0.96	[0.78-1.19]
Time since last night shift (b)												
Never worked at night	5322	6107	1	ref	1669	1769	1	ref	3652	4337	1	ref
0-2 years	206	178	1.26	[1.02-1.55]	118	93	1.41	[1.06-1.88]	88	85	1.11	[0.82-1.52]
3-9 years	123	131	1.09	[0.84-1.40]	68	63	1.21	[0.84-1.72]	55	68	0.97	[0.67-1.41]
10-19 years	172	185	1.10	[0.88-1.36]	85	79	1.22	[0.88-1.68]	87	106	1.01	[0.75-1.36]
≥ 20 years	268	328	1.07	[0.90-1.27]	52	55	1.11	[0.74-1.65]	216	273	1.05	[0.87-1.27]
Intensity of night work (nights/week) (c)												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<1 nights/week	122	135	0.94	[0.73-1.21]	62	54	1.31	[0.89-1.93]	60	81	0.73	[0.51-1.03]
1-2 nights/week	254	263	1.01	[0.84-1.22]	108	117	1.03	[0.78-1.36]	146	146	1.01	[0.79-1.29]
≥3 nights/week	132	112	1.26	[0.97-1.63]	68	41	1.80	[1.20-2.71]	64	71	0.92	[0.65-1.31]
Lifetime cumulative number of night shifts (c)												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<300	170	173	1.06	[0.85-1.32]	92	86	1.20	[0.88-1.65]	78	87	0.92	[0.67-1.27]
300-999	174	184	0.99	[0.80-1.23]	87	75	1.27	[0.92-1.76]	87	109	0.78	[0.58-1.04]
≥1000	164	153	1.11	[0.88-1.39]	59	51	1.31	[0.88-1.94]	105	102	1.05	[0.79-1.39]
Number of night hours per week (c)												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<11	150	158	0.99	[0.79-1.26]	69	68	1.19	[0.84-1.70]	81	90	0.87	[0.63-1.19]
11-19	179	195	0.96	[0.77-1.18]	79	82	1.06	[0.76-1.47]	100	113	0.89	[0.67-1.18]
≥20	173	145	1.28	[1.01-1.61]	87	60	1.57	[1.11-2.23]	86	85	1.06	[0.77-1.45]

a Odds ratios calculated using conditional logistic regression models stratified by age group (5-year) and study, and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, Body mass index, alcohol, tobacco, menopausal hormone therapy (all women/postmenopausal women), and menopausal status (all women)

b using data from the 5 studies of the pooled analysis (Australia, Canada, France, Germany, Spain).

c using data from the 4 studies with information on night work intensity (Canada, France, Germany, Spain).

Table 4: Odds ratios for breast cancer combining intensity of night work with duration, length of shifts and time since last night shift, using data from four studies with information on exposure intensity (Canada, France, Germany and Spain).[a]

	All women				Premenopausal women				Postmenopausal women			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Intensity x Duration of night work												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<3 nights/week and <10 yrs	201	218	0.99	[0.81-1.21]	106	99	1.19	[0.89-1.60]	95	119	0.84	[0.63-1.11]
<3 nights/week and ≥10 yrs	175	180	0.99	[0.79-1.23]	64	72	1.01	[0.71-1.45]	111	108	0.98	[0.74-1.30]
≥3 nights/week and <10 yrs	92	80	1.23	[0.90-1.67]	52	34	1.66	[1.05-2.60]	40	46	0.88	[0.57-1.37]
≥3 nights/week and ≥10 yrs	40	32	1.34	[0.83-2.15]	16	7	2.55	[1.03-6.30]	24	25	1.00	[0.56-1.77]
Intensity x Length of night shift												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<3 nights/week and shift<10hrs	200	217	0.96	[0.78-1.17]	78	93	0.96	[0.69-1.32]	122	124	0.98	[0.75-1.27]
<3 nights/week and shift≥10hrs	173	179	1.03	[0.82-1.27]	91	78	1.28	[0.93-1.77]	82	101	0.83	[0.61-1.13]
≥3 nights/week and shift<10hrs	60	47	1.34	[0.91-1.98]	28	21	1.56	[0.86-2.80]	32	26	1.17	[0.69-1.99]
≥3 nights/week and shift≥10hrs	69	55	1.35	[0.93-1.94]	38	18	2.15	[1.21-3.84]	31	37	0.9	[0.55-1.48]
Intensity x Time since last night shift												
Never worked at night	4373	4634	1	ref	1393	1437	1	ref	2979	3196	1	ref
<3 nights/week and time≤2 years	121	106	1.16	[0.89-1.52]	68	59	1.28	[0.89-1.85]	53	47	1.07	[0.71-1.60]
<3 nights/week and time>2 years	255	291	0.93	[0.78-1.11]	102	112	1.03	[0.77-1.37]	153	179	0.87	[0.69-1.09]
≥3 nights/week and time≤2 years	44	21	2.21	[1.30-3.76]	28	12	2.76	[1.38-5.53]	16	9	1.58	[0.68-3.64]
≥3 nights/week and time>2 years	88	91	1.04	[0.77-1.41]	40	29	1.43	[0.87-2.35]	48	62	0.82	[0.55-1.21]

[a] Odds ratios calculated using conditional logistic regression models stratified by age group (5-year) and study, and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, body mass index, alcohol, tobacco, menopausal hormone therapy (all women/postmenopausal women), and menopausal status (all women)

Table 5: Odds ratios for breast cancer subtypes in ever versus never night workers. Pooled analysis of Breast Cancer and Night Work in Five Studies [a] [b]

Night Work	All women				Premenopausal women				Postmenopausal women			
	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
ER-positive												
Never night work	3970	6107	1	ref	1231	1769	1	ref	2738	4337	1	ref
Ever night work	602	826	1.19	[1.06-1.33]	258	290	1.36	[1.12-1.64]	344	536	1.09	[0.93-1.26]
ER-positive / HER2-positive												
Never night work	378	6107	1	ref	126	1769	1	ref	252	4337	1	ref
Ever night work	73	826	1.70	[1.30-2.23]	32	290	1.77	[1.16-2.70]	41	536	1.59	[1.11-2.28]
ER-positive / HER 2-negative												
Never night work	2956	6107	1	ref	919	1769	1	ref	2036	4337	1	ref
Ever night work	443	826	1.15	[1.01-1.30]	192	290	1.35	[1.10-1.66]	251	536	1.03	[0.87-1.22]
ER-negative												
Never night work	865	6107	1	ref	300	1769	1	ref	565	4337	1	ref
Ever night work	93	826	0.82	[0.65-1.04]	40	290	0.90	[0.62-1.30]	53	536	0.79	[0.58-1.07]

[a] Odds ratios calculated using conditional logistic regression models stratified by age (5-year) and study, and adjusted for age at menarche, parity, age at first full term pregnancy, breastfeeding, family history of breast cancer, oral contraceptive use, body mass index, alcohol, tobacco, menopausal hormone therapy (all women/postmenopausal women), and menopausal status (all women).

[b] Seventy-six cases had missing data for ER status and 181 for HER-2 status