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RESEARCH ARTICLE

The impact of night shift work on breast cancer: Results from the Burden of Occupational Cancer in Canada Study

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Abstract

Background: We estimated the proportion and number of female breast cancer cases in Canada attributable to night shift work, a probable cause of breast cancer.

Methods: Levin's equation was used to calculate population attributable fractions (PAFs) among Canadian women who ever worked night/rotating shifts from 1961 to 2000, accounting for labor turnover and survival to the year 2011. The calculated PAFs were applied to 2011 Canadian breast cancer incidence statistics to obtain the number of attributable cases.

Results: Approximately 1.5 million women ever worked night/rotating shifts during 1961-2000 and survived to 2011. The PAFs ranged from 2.0% (95% confidence interval [CI]: 1.4-6.2) to 5.2% (95% CI: 3.7-13.6), and 470 to 1200 incident breast cancer cases in 2011 were likely due to shift work, of which 38% would have been diagnosed among women in health-related occupations.

Conclusions: More research is needed to increase the certainty of this association, but current evidence supports workplace-based prevention.

KEYWORDS

breast cancer, burden, night shift work, occupational cancer, population attributable fraction

1 | INTRODUCTION

Breast cancer is the most common cancer in women worldwide.[1] There are numerous known risk factors for breast cancer, including older age, lifestyle factors, reproductive and hormonal factors, and family history, among others.[2] In 2007, "shift work involving circadian disruption" was classified by the International Agency for Research on Cancer (IARC) as a probable cause of female breast cancer (IARC Group 2A)[3] based on sufficient animal and limited epidemiological evidence.

The proportion of disease that could be prevented by decreasing population exposure to modifiable risk factors, a concept known as "population attributable fraction" (PAF), can help identify where and for whom preventative disease-specific interventions need to be focused. PAFs are determined by the proportion of the population exposed to the risk factor and the disease rates in that population, both of which are country- and time-period specific. For instance, Brown et al[4] estimated that 23% of 2015 breast cancer cases could have been prevented in UK women through breastfeeding, and not drinking alcohol, being obese or overweight, or using post-menopausal hormones.[4]

Few studies have been conducted on assessing the burden of breast cancer associated with suspected occupational risk factors. Shift work is common throughout the industrialized world and has emerged as potentially the most important occupational cause of breast cancer. Estimates from previous burden studies based on the application of the PAF indicate that the impact of shift work on breast cancer could be substantial. In the United Kingdom, approximately 4.5% (95% confidence interval [CI]: 3.2-5.9) of breast cancers annually could be due to shift work.[5] A separate study conducted in the United States, which adapted the UK method, found that 5.7% (lower and higher estimates: 0.0-11.9) of all incident breast cancer cases each year may be due to shift work.[6]

The objective of this study was to estimate the burden of breast cancer due to shift work among Canadian women. Men were not included due to a lack of evidence regarding shift work and male breast cancer. This study was part of a larger investigation of the burden of cancer in Canada attributable to occupational exposure to 33 different carcinogens.

2 | MATERIALS AND METHODS

2.1 | Overall approach and estimation of the working population

The UK burden of occupational cancer study served as a model for this analysis.[7] As in the UK study, we defined "burden" as the fraction of incident cancer cases attributed to associated occupational carcinogen exposures in the general population; here, this was exposure to shift work involving nights, which is the work schedule associated with circadian disruption. Levin's equation[8] was used to calculate the PAF:

$$\mathrm{PAF} = \frac{\mathrm{PrE} \times (\mathrm{RR}-1)}{\mathrm{PrE} \times (\mathrm{RR}-1) + 1},$$

where PrE was the proportion of the female working population who ever worked shifts involving nights during a risk exposure period (REP), and RR is the relative risk representing the association between shift work involving nights and female breast cancer incidence. Because shift work is a probable breast carcinogen according to IARC,[3] a range of PAF values were calculated using low and high estimates of the RR.

The year 2011 was selected as the target year to estimate burden. This was the most recent year of available Canadian census data at the time of the study. To account for latency, we assumed that working night shifts between 1961 and 2000, inclusive, may contribute to newly diagnosed breast cancers in 2011. This 40-year period was defined as the REP. The PrE was the proportion of the number of women who ever worked shifts during the REP and who survived to 2011 (N_{eREP}) out of the total number of women working during the REP who survived to 2011 (N_{pREP}). The derivation of the PrE value and the selection of low and high RR estimates are described below.

A model of the Canadian working population was developed to estimate the number of workers ever exposed during the REP (the N_{eREP}), integrating information from the exposure assessment step above with data from multiple national population censuses, labor force surveys, and life tables.

We first obtained population census data from Statistics Canada on the number of women used by industry, occupation, and province, in the years 1961, 1971, 1981, 1991, and 2001. Linear interpolation between these census years produced annualized employment estimates. Next, applying the shift work prevalence from the job-exposure matrix (JEM) resulted in estimates of the number of women who worked night shifts in each year of the REP.

To account for labor turnover, the annual proportion of new hires was estimated based on data from national Labour Force Surveys, and applied to our population model. Only new hires aged 15 to 44 years who had worked for at least 1 year were included, to exclude short-term workers. After applying survival rates calculated from Canadian life tables, the total number of shift workers in 1961 who survived to the target year, and the number of exposed new hires in each subsequent year of the REP who survived to the target year, were summed to the N_{eREP}.

The N_{eREP} was then divided by the total female population aged 25 years or older alive in 2011 (or, the population ever of working age during the REP, N_{pREP}) which resulted in the PrE value in Levin's equation. Additional details of the estimation of the working population have been described previously.[9]

2.2 | Night shift work exposure assessment

Night shift work was defined as a work schedule of rotating shifts including nights or of permanent night shifts. This shift work definition is consistent with the one used in most epidemiological

studies and with the RRs we selected for Levin's equation (see Section 2.3). The 1996 Survey of Labour and Income Dynamics (SLID) was used to create a JEM of shift work prevalence by industry and occupation among women. The SLID was a recurrent cross-sectional household survey of a sample of Canadians (about 34 000 households).[10] The pertinent SLID question enquired survey respondents or their proxies on type of work schedule at the end of the year/end of job for the job held in the current year.

The shift work JEM included, by industry and occupation, the number and percent of jobs ever exposed to regular night or rotating shifts. Only jobs held for 20 hours or more per week were considered to exclude jobs which would not have been reported in the long form census (the source of our employment data). Census respondents who worked multiple jobs reported the job at which they worked the most hours. Industries and occupations had been coded in the 1996 SLID using the Standard Industrial Classification (SIC) 1980 and the Standard Occupational Classification (SOC) 1991. These codes were converted to Standard Industrial Classification 1970 and the Canadian Classification and Dictionary of Occupations (CCDO), for integration into the historical working population model built for the larger burden study.

2.3 | Selection of relative risks

The RRs in Levin's equation were selected from pooled effect sizes (ES) based on a review and quality assessment of meta-analyses on shift work and breast cancer risk.[11] A search was conducted on PubMed and Embase for meta-analyses published from 2007 to 2017 without language restrictions. To be included, meta-analyses must have reported at least one pooled ES for breast cancer incidence or mortality risk associated with any night shift work exposure metric. The stated objectives, methods, and conclusions of each meta-analysis were extracted. Pooled ESs from each meta-analysis were ascertained and organized by various study characteristics (eg, night shift work exposure metric, study quality, adjustment for confounders, etc.), which also helped to ensure they were portable to the Canadian context. The AMSTAR 2 critical appraisal checklist[12] was used to rate the methods and reporting of each meta-analysis and to inform the selection of appropriate RRs. In the checklist, the term "intervention" was replaced with "night shift work exposure", and "comparator group" with "any shift work schedule aside from night shift work".

2.4 | Calculation of PAFs and their 95% confidence intervals

Monte Carlo simulation was used to estimate 95% CI for the low and high PAF values. Random samples were drawn from the distributions of each of the two components in Levin's equation (ie, RR and PrE). The variance of the RR component was estimated based on the RR point estimate and its 95% CI as reported in the selected meta-analysis. The PrE was assumed to follow a log-normal distribution with a constant geometric standard deviation set to 2.7. Ten thousand samples were drawn from both the RR component and the PrE component. The 2.5th and 97.5th percentiles of the resulting PAFs were used as the 95% CI lower and upper limits, respectively.

2.5 | Calculation of the number of attributable breast cancer cases

The number of attributable breast cancer cases was estimated by applying the calculated PAFs to the number of registered incident breast cancer cases reported in 2011 in women aged 25 years or older. The 2011 Canadian Cancer Statistics, which are based on cancer registry data collected in Canada,[13] was used as the source of data on 2011 cancer incidence.

3 | RESULTS

3.1 | Shift work exposure assessment

In the shift work JEM applied to the working population, a total of approximately 5 532 000 jobs were held by women in the year 1996. Of these jobs, an estimated 10.0% (n = 553 200) involved regular night or rotating shifts.

3.2 | Estimation of working population

The number of women assessed as ever working regular night or rotating shifts steadily increased over the REP (Figure 1). Approximately 160 500 women ever worked regular night or rotating shifts in 1961; by the year 2000, this number increased to just over 650 000. Approximately 1 505 800 women ever worked regular night or rotating shifts during the REP and survived to the year 2011 (N_{eREP}). The distributions of the N_{eREP} by top 10 major industries and occupations are presented in Table 1. The total number of women aged 25 years or older who were alive in 2011 and who were ever of working age during the REP was 12 185 200 (N_{pREP}). Therefore, the PrE was an estimated 12.4%.

3.3 | Selection of relative risks

Seven meta-analyses were identified from the literature search. These papers, published from 2013 to 2016, collectively included 15 cohort and 16 case-control studies spanning 1996-2016. The most commonly reported exposure metric in meta-analyses was "ever versus never-night shift work",[11] which corresponded to the level of precision available in the shift work JEM. One meta-analysis addressed the greatest number of AMSTAR 2 critical quality domains primarily because it rigorously appraised risk of bias; however, it did not include pooled ESs for ever- vs never-night shift work exposure and breast cancer risk.[14] Two meta-analyses,[15,16] restricted to cohort studies, were excluded from further consideration because pertinent evidence from case-control designs were not considered, and most reviewed cohorts focused on nonoccupational risk factors, leading to

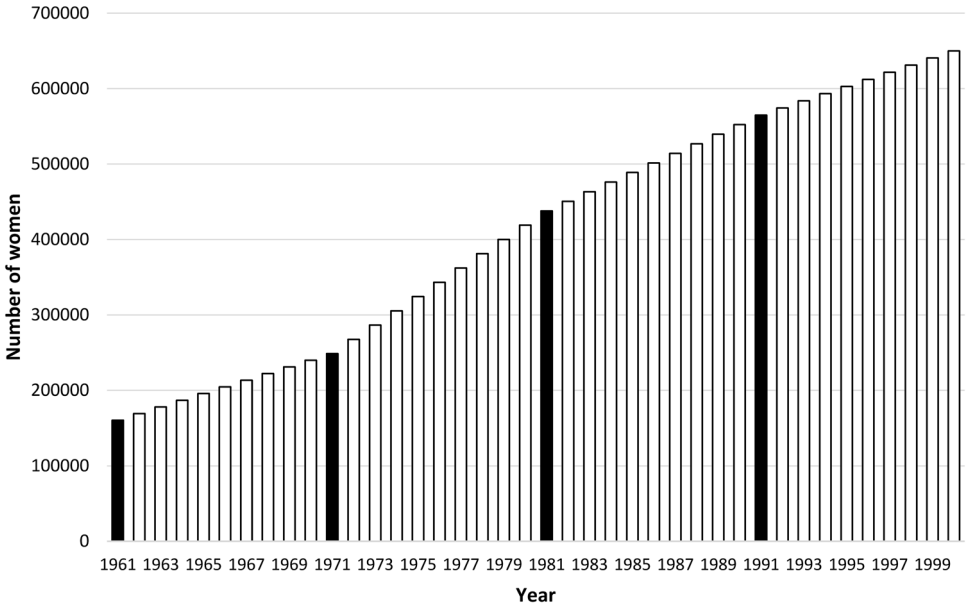

FIGURE 1 Estimated number of Canadian women who ever worked regular night or rotating shifts in each year of the risk exposure period (1961-2000). Black bars represent years when the Canadian census of population was administered (1961, 1971, 1981, and 1991). White bars represent years of interpolated data

a lack of information on shift work exposure assessment. The systematic review and meta-analysis by Jia et al[17] was the only study to provide pooled estimates restricted to high-quality studies and studies that adjusted for multiple covariates: random effects pooled ESs ranged from 1.15 (95% CI: 1.05-1.25, $n = 9$ studies adjusted for ≥4 major confounding factors) to 1.40 (95% CI: 1.13-1.73, $n = 9$ high-quality studies).[17] We, therefore, assumed that these pooled ESs spanned the possible range of risks for night shift work and breast cancer, and used the bounds from Jia et al[17] as the lower and higher estimates of the RR in Levin's equation, respectively.

TABLE 1 Estimated N_{eREP}, and number and proportion of incident breast cancer cases attributable to working regular night or rotating shifts between 1961 and 2000, top 10 major industries, Canada, 2011

			Incident breast cancer cases in 2011		
	N_{eREP}[b]		Cases attributable to night shift work (N)[c]		
Major industry[a]	N[c]	Proportion of N_{eREP} (%)[d]	Low estimate	High estimate	Proportion of total number of cases (%)[d]
Health care/social assistance	601 000	40	200	520	43
Accommodation and food services	324 500	22	90	220	18
Trade	183 000	12	50	140	11
Manufacturing	146 800	10	50	130	11
Public administration	43 900	3	15	40	3
Finance/insurance/real estate and leasing	41 800	3	15	35	3
Other services	41 400	3	15	35	3
Information/culture/recreation	38 300	3	10	30	2
Business/management/other support	31 900	2	10	20	2
Transportation/warehousing	16 900	1	5	15	1

[a]North American Industry Classification System (2002) derived industry categories.
[b]Number of women who worked permanent night or rotating shifts between 1961 and 2000 and who survived to 2011.
[c]Total does not add up to counts reported in text due to rounding and the exclusion of industries not in the top 10.
[d]Total does not add up to 100% due to rounding and the exclusion of industries not in the top 10.

3.4 | PAF and number of attributable breast cancer cases

Using Levin's equation, we estimated a low PAF of 2.0% (95% CI: 1.4-6.2) and a high PAF of 5.2% (95% CI: 3.7-13.6). Since there were approximately 23 200 cases of breast cancer diagnosed among women in Canada in the year 2011,[12] these PAFs corresponded to an estimated 470 (95% CI: 330-1400) to 1200 (95% CI: 860-3200) incident cases due to night shift work.

3.5 | By industry

The largest number and proportion of attributable incident breast cancer cases occurred among women working in health care and social assistance (43% of attributable cases). Relatively smaller proportions of attributable cases were diagnosed in women in the accommodation and food services sector (18%), trade (11%), and manufacturing (11%). The remaining attributable cases were distributed among women in several other industries (Table 1).

3.6 | By occupation

An estimated 180 to 460 (38%) of attributable breast cancers would have been diagnosed among women working in health-related jobs, particularly in nursing. Approximately 16% of attributable cases would have occurred in women who are chefs and cooks, or who work in food services. Women employed in sales and service occupations could have accounted for nearly 9% of attributable cases. The remaining attributable cases were diagnosed among women in all other occupations combined (Table 2).

4 | DISCUSSION

Shift work has an important impact on breast cancer incidence in Canadian women. In this study, an estimated 2.0% to 5.2% of newly diagnosed breast cancer cases were probably attributable to shift work involving nights, amounting to approximately 470 to 1200 incident cases in 2011. The burden was estimated to be largest among women working in health-related occupations, where women constitute nearly 80% of the labor force and 40% of all attributable breast cancer cases would have occurred. Our PAF estimates are comparable to the PAF values estimated in the United Kingdom[5] and the United States (4.5%-5.7%).[6]

As with burden studies conducted in other jurisdictions, the PAF approach used here entailed multiple assumptions due to the limitations of available exposure, epidemiological, and historical labor force data.

Epidemiologic studies of shift work and breast cancer risk have used a variety of exposure metrics. Although some studies found that a longer duration (ie, number of years) of rotating and night shift work is positively associated with breast cancer risk,[18,19] the evidence is relatively more consistent for "ever vs never" shift work, and we lacked data on the distribution of lifetime employment durations in jobs involving shift work. There is also sparse and inconsistent evidence for shift work frequency (number of nights per year), cumulative exposure (number of lifetime nights), age when worked shifts involving nights, and specific shift start and end times. Use of available "ever vs never" shift work data, although a simplistic exposure metric, circumvented these uncertainties and resulted in more readily interpretable PAF estimates.

We were able to obtain detailed, nationally representative estimates of job-specific shift work prevalence using data from the 1996 SLID. Given the lack of historical survey data on shift work, we assumed job-specific shift work prevalence to be constant over the REP. In our working population model, the use of simple linear interpolation between censuses did not account for yearly fluctuations that typically occur in labor markets. Thus, we are likely underestimating the uncertainty of our estimates, but these are not influential sources of bias in burden estimation.[20] Grouping industries and occupations, while primarily done to minimize data suppression, helped to avoid missing shift workers from the JEM.

In the absence of precise epidemiological data, we assumed a latency of 10 to 50 years between shift work and breast cancer.[20] If the real latency period is shorter, then an over-estimation of the burden estimate is likely. The REP used in this study (1961-2000), however, captured the range of years of shift work exposure that could theoretically result in a breast cancer diagnosis in the year 2011.

A major source of uncertainty was the RRs in Levin's equation. Pooled ESs used as high and low RRs in the PAF model were based on epidemiological studies relevant to the Canadian context but with significant between-study heterogeneity, varying quality, and possible uncontrolled confounding.[17] One contributor to heterogeneity was night work exposure assessment; a variety of methods were used, most commonly self-report/JEM, but also census and registry-based job history data. As one meta-analysis suggested,[21] pooled estimates of breast cancer risk may differ according to the method of night shift work exposure assessment used in the reviewed epidemiological studies. These differences are also likely to be influenced by the adjustment for confounding variables, and by the included study populations, occupations, and industries, which are among other potential contributors to heterogeneity in meta-analyses. Additionally, definitions of shift work were not stated in approximately half of the studies included in pooled ESs, shift work exposure categories varied across studies, and residual exposure misclassification was a possibility, albeit likely nondifferential in case-control studies.[22] Studies excluded from the high-quality subgroup analysis generally lacked shift work exposure or control group definition, or participation rate or duration of follow-up data.[17] The subgroup analysis of studies used as the low RR in our model, included studies that adjusted for four or more out of fourteen confounding factors considered. Although the same nine studies were used for both subgroup analyses,[17] different risk estimates were used to calculate the pooled ESs used as high and low RRs. The high and low RR employed largely captured the range of elevated risks reported in the epidemiological literature.

This study has several strengths that build on and advance previous approaches to estimating the burden of shift work on breast cancer and leverages the richness of national survey data available in

TABLE 2 Estimated N_eREP, and number and proportion of incident breast cancer cases attributable to working regular night or rotating shifts between 1961 and 2000, top 10 major occupations, Canada, 2011.

			Incident breast cancer cases in 2011		
	N_{eREP}[b]		Cases attributable to night shift work (N)[c]		
Major occupation[a]	N[c]	Proportion of N_{eREP} (%)[d]	Low estimate	High estimate	Proportion of total number of cases (%)[d]
Professional occupations in health, nurse supervisors, and registered nurses	311 700	21	100	270	22
Technical, assisting, and related occupations in health	217 000	14	80	190	16
Chefs and cooks, and occupations in food and beverage service	265 000	18	70	190	16
Sales and service occupations (not elsewhere classified)	145 000	10	45	110	9
Machine operators and assemblers in manufacturing	95 600	6	35	90	7
Retail salespersons, sales clerks, and cashiers	92 800	6	25	70	6
Clerical occupations, including supervisors	69 700	5	25	60	5
Other management occupations	81 700	5	25	60	5
Wholesale, technical, insurance, and real estate sales specialists	65 400	4	20	50	4
Laborers in processing, manufacturing, and utilities	34 400	2	10	30	2

[a]National Occupational Classification for Statistics (2006) derived occupational categories.
[b]Number of women who worked permanent night or rotating shifts between 1961 and 2000 and who survived to 2011.
[c]Total does not add up to counts reported in text due to rounding and the exclusion of industries not in the top 10.
[d]Total does not add up to 100% due to rounding and the exclusion of occupations not in the top 10.

Canada. Previous studies have produced a single estimate of burden for breast cancer. Here, producing a range of PAF estimates accounted for uncertainties surrounding the carcinogenicity of shift work for the breast. Relative risks in the PAF equation were selected from a comprehensive review and quality assessment of recently published systematic literature reviews and meta-analyses. In all, our burden model was developed with the highest level of detail available on historical shift work exposure among the female working population in Canada, as well as the most current summary findings on shift work and breast cancer epidemiology.

More research on potential mechanisms linking shift work and breast cancer may influence the interpretation of burden results for breast cancer prevention.[23] It is unclear if there is a threshold of night shifts associated with circadian disruption—the key element believed to be associated with elevated breast cancer risk. The "melatonin hypothesis" postulates that light at night exposure disrupts the endogenous nocturnal release of melatonin, a hormone with tumor-suppressing effects.[24] It is linked to the suspected role of chronodisruption, broadly defined as a disturbance of temporal organization or order of physiology, endocrinology, metabolism, and behavior.[25] Recent research has shown potential modifying effects of chronotype,[26,27] certain circadian gene variants,[28,29] and tumor hormone receptor status.[18,30,31] The potential pathways are interrelated and others may be involved, rendering the biological basis complex and in need of further investigation.

The calculation of a PAF assumes that exposure to night shift work can theoretically be eliminated. Elimination should be pursued where feasible, but where this is not possible (ie, in health care and protective services occupations), the circadian disrupting effects of night shift work may be reduced by interventions that address phase shift, sleep, lifestyle factors, and/or vitamin D exposure.[25] There is evidence from workplace-based interventions that forward-rotating shifts (ie, mornings to afternoons to evenings) that are rapid (ie, with short intervals for each period worked) are associated with improved sleep quality and quantity.[32] Workers who have some input in their shift schedules may have better sleep[33] and possibly select shift schedules based on their chronotype and previous shift work experience,[34] which could decrease their cumulative lifetime exposure to night shifts if self-identified "morning larks." Controlled light and behavioral interventions show less consistent effects on health or melatonin levels, but remain promising avenues for additional prevention research.[35-37]

In summary, an estimated 2.0% to 5.2% of newly diagnosed breast cancer cases in 2011 in Canada were attributed to shift work. This corresponds to approximately 470 to 1200 incident cases of breast cancer, annually, that are potentially preventable. High-quality epidemiologic studies that better address exposure and potential confounding would help to clarify the true relationship between night shift work and breast cancer risk and thereby improve burden estimation. Future research on occupational cancer burden should include shift work, despite its current status as a probable human carcinogen, as there is a need to quantify its possible contribution to breast cancer around the world.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

MP and FL are first coauthors who contributed equally to this paper with respect to the selection of relative risks in Levin's equation, interpreting the results, and writing. MAH and JK acquired the data for and conducted the shift work exposure assessment, with input and review from FL, CEP, VHA, HD, and PAD. JK led the development of the population model with input from CBM, FL, and PAD. CS conducted the final analyses and developed the method for estimating 95% confidence intervals. PAD conceptualized the adaptation of the UK burden of occupational cancer study to the Canadian context and is the Principal Investigator of the burden of occupational cancer in Canada study. All authors critically revised this study for important intellectual content, approved the final version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved.

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