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Shift work, body mass index and associated breast cancer risks in postmenopausal women

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Abstract

Introduction and Objective. Shift work increases the risk of breast cancer, but the mechanisms is still under discussion. This study evaluates the relationship between breast cancer and shift work on the basis of overweight and obesity among postmenopausal women.

Materials and method. We examined this association using data from a case–control study carried between 2015 and 2019. The study involved 111 postmenopausal women with breast cancer and the same number of control participants. A self-reporting questionnaire was used for data collection. Multivariate logistic regression was conducted to find correlations between variables and determine the strength of relationships.

Results. A 2.65-fold risk of breast cancer (OR=2.65; 95% CI: 1.34–5.22) was found among shift work women, compared with postmenopausal women not performing shift work. The association was modified by body mass index, showing a risk rate 9.84 times higher (OR=9.84; 95% CI: 2.14–45.19) among shift work and overweight women, compared to non-overweight women who had never been shift workers.

Conclusions. About 49% of controls and 72% of cases had ever worked in a job that required shift work. The risk of breast cancer in postmenopausal women is associated with shift work, especially among overweight women. Some preventive measures to reduce the risk of breast cancer, in particular regarding a healthy lifestyle and weight control in this group of working women, should be implemented.

Key words

obesity, breast cancer, shift work, BMI, overweight, case-control study, postmenopausal women

INTRODUCTION AND OBJECTIVE

One of the most common oncological diseases among women is breast cancer (BC). The cause of breast cancer is multifactorial and several risk factors for this cancer are differentiated into non-modifiable risk (e.g. age, gender, genetic), place of residence and environmental factors. The most well-defined environmental risk factors are radiation exposure, environmental pollutants and toxic chemicals. However, lifestyle is the leading risk factor. Risk is increased by excessive alcohol consumption, physical inactivity, obesity, high-fat diets, and smoking [1, 2]. The authors of several studies emphasize that occupational factors may increase the incidence of breast cancer [3, 4], and night shift work may be a potential risk factor for this type of cancer [5]. In 2007, the International Agency for Research on Cancer (IARC) concluded that night shift work (NSW) is a probable carcinogen due to circadian disruption based on sufficient evidence from animal studies and limited evidence from epidemiological studies. In 2019, the IARC described NSW as a 'probable' carcinogen (IARC Group 2A) [6, 7].

Although some studies show that night shift work increases the risk of developing breast cancer, the mechanisms by which this occupational factor may be responsible for the development of cancer are still unknown. A recent published review shows that shift work increases the risk of BC in the female population, specifically for women who start night work before menopause. However, in limited studies, women who start night work after menopause, the shift work does not affect BC [8]. Additionally, shift workers have an increased risk of being overweight or obese [9]. Therefore, there are gaps in knowledge about whether a factor such as body weight modifies the risk of breast cancer in shift workers, particularly in postmenopausal women. Such findings would be of interest to clinical trials evaluating the role of weight loss interventions in reducing the risk of breast cancer in postmenopausal women.

The aim of this study was to investigate the relationship between shift work and breast cancer risk on the basis of overweight and obesity among postmenopausal women, with adjustment for potentially confounding factors.

MATERIALS AND METHOD

Study design and patient selection. The case-control study was carried out in 2015 – 2019 in the Łódź Province in central Poland. The study group included 111 postmenopausal women, patients of oncology departments and clinics, diagnosed with malignant breast cancer. The criterion for including women in the case group were histologically-confirmed breast cancer. Because the crucial predictor was

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shift work, the final number of respondents was limited to 111 women who answered questions about shift work. The community-based control group included postmenopausal healthy women (N=111) who did not have breast cancer, on the basis of the following criteria*:* no history of breast or any other cancer. The control group consisted women similar in characteristics to the women from the study group in terms of age (±3 years) and education.

The study was approved by the Ethics Committee at each participating institution and the Bioethics Committee of the Medical University in Łódź (Approval No. RNN/236/15/EC, dated 22 September 2015). All participants provided written informed consent prior to enrolment in the study.

MATERIALS AND METHOD

The research tool was an anonymous and voluntary questionnaire. A structured questionnaire was developed to obtain demographic information and data on socio-economic status, anthropometric data, lifestyle (alcohol consumption, smoking, physical activity, diet, stress exposure), reproductive history (pregnancy history, menstruation and menopause, pregnancy prevention, hormonal treatment), employment history (shift work), and family history of cancer. Before starting the main study, a pilot study was conducted among 15 patients from the case group and 15 women from the control group to check the reliability of the questionnaire.

Anthropometric Data. Detailed body size data was collected from study participants, including their weight (kg) and height (m). Body-mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. BMI was classified using the following cut-off values: 18.5–24.9 kg/m^2 – normal, 25.0–29.9 kg/m^2 – overweight, and ≥ 30 kg/m^2 – obese.

Shift Work. In relation to shift work, information was collected on type of job, year of commencing employment, start and end each shift in a normal week, rotation of shift work (forward/backward), number of consecutive night shifts, average number of nights per month, and average number of years worked. Shift was defined as a shift including evening/night, rotating or other types of shifts. Ever shift workers were women who reported ever having worked in evening/night, rotating or other types of shifts.

Focusing on the total duration of shift work, 3 categories were defined: never shift work (reference group), <5 years of work, including night shifts, and ≥5 years of shift work, including night shifts. The intensity of shift work during the worker's career was also classified into 3 levels: never shift work (reference group), under 6 years, and 6 years and longer.

Statistical Methods. In the descriptive part of statistical analysis, the numbers of each group and their structure indicators were given. As the variables analysed were not normally distributed, the median and quartile range (IQR) values were provided in the descriptive analysis. An analysis of the significance of differences in the abundance of each subgroup was performed using Chi2 Pearson test. Smoking as an independent variable was analysed for its impact on the study variables, but was not included in the further analysis due to lack of statistical significance.

Multivariate logistic regression was used to find eventual correlations and level of the effects of independent variables upon the parameters of interest, adjusted for age, age at first menstrual period, age of natural menopause, breast feeding and categorical BMI. The Odds ratios (OR) and 95% confidence intervals (CI) were calculated respectively. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using STATISTICA 13.0 software (StatSoft, Kraków, Poland).

RESULTS

Table 1 shows baseline characteristics of participants for the 2 groups: shift workers and non-shift workers among controls and cases. About 49% of controls and 72% of cases had ever worked in a job that required shift work. Shift workers in the control group were older (median 63.0; IQR 10.7 years vs 58.2; IQR 12.92), more frequently obese (43.6% BMI ≥ 30 vs 30.4%) and current smokers (27.3% vs 11%), compared with those who had never been exposed. The group of shift workers among cases lived more often in rural areas (24% vs 22.6%) and were more often overweight (37.5% vs 35.5), compared to non-shift workers. They were more likely to never smoked (37.5% vs 29.0%). Smaller or no differences were observed for age at menarche, age of first birth, duration of breastfeeding, and age at natural menopause. Short sleep duration (average <6 hours per 24-hour period) were reported by 27.3% of controls employed in shift work and 30% cases who report working shifts.

Multivariate logistic regression models show that having ever performed shift work was associated with a higher breast cancer risk among postmenopausal women, compared to subjects never employed in shift work (OR=2.65; 95% CI: 1.34–5.22). Shift work duration showed a dose response trend toward increasing the risk of breast cancer. A higher number of working years in shifts was associated with a higher risk for breast cancer (≥5 years: OR=3.43; 95% CI: 1.54–7.67). Number of shifts per month was also associated with a risk of breast cancer. The highest OR was observed among those with the shorter intensity (<6 times/month) of exposure (OR=2.73; 96% CI: 1.15–6.52). Obesity (BMI=30 or more kg/m^2) doubled the risk of breast cancer (OR=2.18; 95%CI: 1.04–4.66), while overweight (BMI=25 – 29.9 kg/m^2) increased 3.5-fold (OR=3.51; 95%CI: 1.81–8.86) the risk of developing breast cancer (Tab. 2).

The association between shift work and breast cancer was modified by body mass index. Compared to non-overweight (BMI<25 kg/m^2) and never shift work postmenopausal women, non-overweight shift work women had a statistically significant elevated risk of breast cancer of 6.48 (95% CI: 1.30–32.39), while for overweigh women (BMI=25 – 29.9 kg/m^2) the risk was OR=9.84 (95% CI: 2.14–45.19), respectively. Postmenopausal women with obesity (BMI=30 or more kg/m^2) who employed in shift work had a 5-fold higher risk of breast cancer (OR=5.08; 95%CI: 1.12–22.97), compared to non-overweight postmenopausal women who had never worked shifts (Tab. 3).

Table 1. Distribution of characteristics of study variable

Patients	Controls (N, %)		Cases (N, %)		p value
	Non-shift work	Shift work	Non-shift work	Shift work	
Population	56 (50.45)	55 (49.55)	31 (27.93)	80 (72.07)	¾
Age (median; IQR)	58.2 (12.92)	63.0 (10.07)	66.9 (12.50)	66.0 (8.52)	0.000
Place of residence (No. of inhabitants)					
rural	21 (37.50)	20 (36.36)	7 (22.58)	24 (30.00)	0.162
cities <50 th	10 (17.86)	18 (32.73)	5 (16.13)	16 (20.00)	0.270
cities 50–100 th.	14 (25.00)	9 (16.36)	10 (32.26)	17 (21.25)	0.530
cities >100 th.	11 (19.64)	8 (14.55)	9 (29.03)	23 (28.75)	0.042
Smoking					
never	33 (58.93)	21 (38.18)	9 (29.03)	30 (37.50)	0.047
past	17 (30.36)	19 (34.55)	14 (45.16)	29 (36.25)	0.337
current	6 (10.71)	15 (27.27)	8 (25.81)	21 (26.25)	0.208
Age at first menstruation (median; IQR)	14.0 (2.00)	14.0 (1.00)	13.0 (3.00)	13.0 (2.00)	0.323
Age of first-born child (median; IQR)	22.3 (4.52)	21.6 (5.25)	22.3 (3.81)	21.5 (3.95)	0.323
Breastfeeding duration (months.median; IQR)	5.0 (4.00)	5.0 (2.00)	6.0 (7.00)	5.0 (1.00)	0.006
Age of natural menopause (median; IQR)	50.0 (4.00)	50.0 (4.00)	50.0 (7.00)	52.0 (4.50)	0.518
Sleep duration (No. of hours)					
<6	4 (7.14)	15 (27.27)	1 (3.23)	24 (30.00)	0.008
≥6	52 (92.86)	40 (72.73)	30 (96.77)	56 (70.00)	0.568
BMI categorical (kg/m^2)					
18,5–24,9	33 (58.93)	16 (29.09)	3 (9.68)	15 (18.75)	0.000
25,0–29,9	6 (10.71)	15 (27.27)	11 (35.48)	3 (37.50)	0.003
≥30	17 (30.36)	24 (43.64)	17 (54.84)	35 (43.75)	0.144

Table 2. Associations of shift work, body mass index and breast cancer risk among postmenopausal women

Factor	Cases (N, %)	Control (N, %)	OR	95% CI	ORa	95% CI
Shift work						
never	31 (27.93)	56 (50.45)	1.00	¾		
ever[b]	80 (72.07)	55 (49.55)	5.82	2.15-15.75	2.65	1.34-5.22
Duration of exposure (years)						
not shift work	31 (27.93)	56 (50.45)	1.00	¾		
<5	39 (35.14)	30 (27.03)	2.16	0.79-5.89	2.11	0.98-4.56
≥5	41 (36.93)	25 (22.52)	3.67	1.38-9.75	3.43	1.54-7.67
Intensity of exposure (times/month)						
not shift work	31 (27.93)	56 (50.45)	1.00	¾		
<6	29 (26.13)	24 (21.62)	3.28	1.14-9.36	2.73	1.15-6.52
≥6	51 (45.94)	31 (27.93)	2.65	1.02-6.87	2.60	1.24-5.46
BMI categorical (kg/m^2)						
18.5–24.9	18 (16.21)	49 (44.14)	1.00	¾		
25.0–29.9	41 (36.94)	21 (18.92)	4.00	1.81-8.86	3.51[c]	1.81-8.86
≥30	52 (46.85)	41 (36.94)	2.23	1.05-4.73	2.19	1.04-4.66

BMI, body mass index; OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, age at first menstrual period, age of natural menopause, breast feeding, categorical BMI
[b] Ever shift workers were women who reported ever having worked in evening/night, rotating or other types of shifts.
[c] Adjusted for age, age at first menstrual period, age of natural menopause and breast feeding.
The association between shift work and breast cancer was modified by body mass index. Compared to non-overweight (BMI<25 kg/m2) and never shift work postmenopausal women, non-overweight shift work women had a statistically significant elevated risk of breast cancer of 6.48 (95% CI: 1.30–32.39), while for overweigh (BMI=25 to 29.9 kg/m2) women the risk was ……..

Table 3. Associations of combined categories of body mass index and shift work for risk of breast cancer among postmenopausal women

Shift work	Body mass index											
	Not-overweight (BMI<25)				Overweight (BMI=25.0–29.9)				Obese (BMI ≥30)			
	Cases (N, %)	Controls (N, %)	ORa	95% CI	Cases (N, %)	Controls (N, %)	ORa	95% CI	Cases (N, %)	Controls (N, %)	ORa	95% CI
never	3 (16.67)	33 (67.35)	1.00	¾	11 (26.83)	6 (28.57)	4.62	0.65–32.79	17 (32.69)	17 (41.46)	2.70	0.43–17.09
everb	15 (83.33)	16 (32.65)	6.48	1.30–32.39	30 (73.17)	15 (71.43)	9.84	2.14–45.19	35 (67.31)	24 (58.54)	5.08	1.12–22.97

BMI, body mass index; OR, odds ratio; CI, confidence interval.
[a] Adjusted for age, age at first menstrual period, age of natural menopause, breast feeding.
[b] Ever shift workers were women who reported ever having worked in evening/night, rotating or other types of shifts.

DISCUSSION

The presented data show that shift work is a risk factor for breast cancer. Compared to postmenopausal women not performing shift work, those with history of shift job had an adjusted odds ratio for breast cancer of OR=2.65 (95% CI: 1.34–5.22). The risk of breast cancer was positively correlated with duration of shift work and intensity (times/month) of exposure.

As early as 1987, Stevens R.G. hypothesized that work at night probably increases the risk of breast cancer (exposure to light at night). This is related to the hypothesis that working at night and exposure to light at night inhibits melatonin synthesis and increases estrogen levels, which may lead to an increased risk of breast cancer [10]. Breast cancer is an etiologically heterogeneous disease. French researchers investigated the association of night work with breast cancer subtypes for the estrogen receptor (ER), the progesterone receptor (PR) and the human epidermal growth factor 2 (HER2) receptor. The study confirms that night work may increase the risk of ER, PR, and HER2-positive breast cancer subtypes, especially in pre-menopausal women [11]. Norwegian researchers made similar observations. The effect of night work on the estrogen- and progesterone-receptor breast cancer risk was assessed in a case-control study. The highest risk was observed for neoplasms with a positive progesterone receptor (OR = 2.4, 95% CI: 1.3, 4.3; P-trend = 0.01) [12].

Most epidemiological studies which have analyzed the relationship between night work and breast cancer risk reported an increased breast cancer risk in night workers [13–15]. Cordina-Duverger et al. analyzed case-control studies and obtained results showing that night work increased the risk of breast cancer in premenopausal women, especially for high frequency of night work and long exposure. The breast cancer odds ratio for women who ever worked at night compared to never night workers was 1.12 [16]. Another epidemiological study in Spain also found an increased breast cancer risk among shift workers. Having ever shift worked was associated with an increased breast cancer risk compared to day workers (OR=1.18; 95% CI: 0.97–1.43) [17]. A systematic review and meta-analysis of 31 prospective cohort studies supported positive associations among night-shift work exposure and breast cancer morbidity (2.9% for total and 8.6% for more than 10 years night-shift work) [18]. A population-based case-control study GENICA found that long-term night work was associated with a modestly increased breast cancer risk (breast cancer risk of 1.73 for women who reported > 807 night shifts [19].

The results of the current study strongly suggest that the association between shift work and breast cancer risk is modified by body mass index. To be more precise, body mass index can increase the breast cancer risk, showing a nine times higher risk among shift work and overweight, postmenopausal women, compared to non-overweight postmenopausal women who had never been shift workers. Some studies show that working at night may be associated with weight and central adiposity. In a study of 40 nurses it was found that shift working women were 3.7 times and 2.9 times more likely to have excessive weight and adiposity, respectively [20]. A cross-sectional study conducted among 724 female nurses and midwives demonstrated that cumulative night shift work showed a significant associations with body mass index [21]. The association of shift work and the obesity risk in nurses was a subject of a systematic review and meta-analysis conducted by Zhang et al. [22]. This study also confirmed that shift work may play a significant role in the development of obesity among shift-working nurses. Many other studies also confirm this relationship [23, 24, 25].

Limitations of the study. A limitation was the self-report questionnaire, although this approach is a valid and reliable tool for lifestyle and workplace surveys. Another limitation may be the sample size, but it was sufficiently powered to detect the difference between the groups, and obtain statistically significant results. The strong point of the study was combining shift work analysis with the impact of body weight on the risk of breast cancer among women after menopause. Overweight/obesity is a risk factor of various cancers. In 2002, the International Agency for Research on Cancer (IARC) reviewed the existing scientific evidence and found a link between body weight and cancer [26]. In 2016, IARC concluded that positive associations between BMI and postmenopausal breast cancer risk have been observed [27].

There are also reports confirming an increased risk of breast cancer in overweight and obese women. A study of 184,931 Asian women found that increase in waist circumference during the menopause correlated with an increased risk of breast cancer [28]. Abdominal obesity is of particular importance. The study by Chung et al. confirmed the importance of not so much obesity as abdominal obesity. In a group of 1,309 women who completed 18 months of follow-up, a significant loss of waist-to-hip ratio (WHR) (5% or more) was associated with a reduced risk of mortality from breast cancer, compared to stable WHR. A higher baseline WHR was also associated with a higher mortality. However, no such correlation was observed for BMI [29]. An association of an increased risk of breast cancer with an increased waist-to-hip ratio has been observed in subsequent studies [30]. In the study by Nagrani et al. WHR ≥ 0.95 was strongly associated with breast cancer in both premenopausal (OR=4.3; 95% CI: +2.9–6.3) and postmenopausal women

(OR=3.4; 95% CI: 2.4–4.8) [31]. In the United States, it has been found that 11,000–18,000 deaths among breast cancer patients over the age of 50 per year could be avoided if women maintained a BMI < 25 [32]. This relationship was also examined in Turkey, where it was shown that patients with diagnosed postmenopausal breast cancer had a significantly higher BMI than the control group in this age group. There was no such relationship in the premenopausal group. In obese postmenopausal women, the breast cancer risk was 3 times higher [33].

So far, it is not fully understood what biological mechanisms cause obesity to increase the risk of breast cancer. A possible cause of this phenomenon could be elevated levels of endogenous hormones and inflammatory factors [34]. Obesity in the postmenopausal period predisposes to increased production of estrogens, which come mainly from adipose tissue. Adipose tissue is also an organ with endocrine secretion of many other biologically active substances, including: insulin-like growth factor (IGF), sex hormones, adiponectin, angiotensin, leptin, and tumour necrosis factor α (TNF-α) [35]. Tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) produced by adipose tissue, increase the oxidative activity of NADPH which activates protein kinase C and NFKB, increasing the body's oxidative stress [36]. Increased levels of oxidants, especially reactive oxygen species (ROS) and reactive nitrogen species (RNS), in excess of the body's antioxidant capacity (so-called oxidative stress), lead to chronic inflammation [37]. There is increasing evidence that chronic inflammation is the leading cause of inflammation, a factor leading to the development and progression of neoplasms. Apart from leptin and hepatocyte growth factor (HGF), adipokines produced by the adipose cell include adiponectin, the increased levels of which inversely correlate with the risk of breast cancer. This relationship has been shown especially in postmenopausal women [38].

CONCLUSIONS

The study has reached some meaningful conclusions which may provide new recommendations for breast cancer prevention in postmenopausal women, and for occupational health professionals to formulate new control and prevention measures. This case-control study found that shift work increases the risk of breast cancer in postmenopausal women, especially those who were overweight. This evidence support the hypothese that shift work may contribute to an increase in body mass index and, consequently, an increased risk of breast cancer. Hence, it may be necessary to take preventive measures to reduce the risk of breast cancer, in particular regarding a healthy lifestyle and weight control in this group of working women, especially in the postmenopausal period. However, a large-scale prospective cohort study is needed to further confirm these conclusions.

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