Research Article

Cancer Epidemiology, Biomarkers & Prevention

# Shift Work Patterns, Chronotype, and Epithelial Ovarian Cancer Risk

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## Abstract

**Background:** Shift work causing circadian disruption is classified as a "probable carcinogen" and may contribute to the pathogenesis of hormone-sensitive cancers. This study investigated shift work exposure in relation to epithelial ovarian cancer (EOC) risk.

**Methods:** In a population-based case–control study with 496 EOC cases and 906 controls, lifetime occupational histories were collected and used to calculate cumulative years of shift work exposure, average number of night shifts per month, and average number of consecutive night shifts per month. ORs and 95% confidence intervals (CI) for associations with EOC risk were estimated using logistic regression. Associations were also examined according to chronotype and menopausal status.

**Results:** More than half of the cases (53.4%) and controls (51.7%) worked evening and/or night shifts. There was no clear pattern of increasing EOC risk with increasing years of shift work; the adjusted OR of EOC comparing the highest shift work category versus never working shift work was 1.20 (95% CI, 0.89–1.63). This association was more pronounced among those self-identified as having a "morning" chronotype (OR, 1.64; 95% CI, 1.01–2.65). Associations did not greatly differ by menopausal status.

**Conclusions:** These results do not strongly demonstrate a relationship between shift work and EOC risk.

**Impact:** This study collected detailed shift work information and examined shift work patterns according to shift times and schedules. The findings highlight that chronotype should be considered in studies of shift work as an exposure.

## Introduction

Ovarian cancer is a deadly disease, ranking as the fifth leading cause of cancer-related death among women in Canada and the United States (1). While the etiology is not well understood, established and strongly suspected risk factors include older age, never use/short duration of use of oral contraceptives, low parity, personal history of breast cancer, family history of breast or ovarian cancer, use of hormone replacement therapy, increased height, and a high body mass index (BMI; refs. 2, 3). Shift work causing circadian rhythm disruption was classified as a "probable carcinogen" by the International Agency for Research on Cancer (IARC) in 2007 (4). In several epidemiologic studies, long-term shift work has been associated with increased cancer risk at multiple sites (5), with the majority of research focused on breast cancer (6–8). The dominant mechanistic focus has been on the "melatonin hypothesis," which postulates that exposure to light at night interferes with circadian rhythms by suppressing melatonin production (9–12) and elevating circulating levels of estrogen, and that if this hormone disruption occurs over many years, the risks of breast and endometrial cancers are increased (13–15). Strong experimental evidence has supported this mechanism and has suggested that this pathway may extend to other hormone-sensitive malignancies, such as epithelial ovarian cancer (EOC; refs. 16, 17).

Four epidemiologic studies have previously assessed shift work exposure in relation to EOC risk (18), two reporting a positive association (19, 20), and two observing no evidence of an association (21, 22). Differences in findings may be related to differences in the sources of data and shift work definitions across these studies that included self-reported occupational history with specific questions about night work (19), current baseline rotating work (20), self-reported years of working rotating shifts with nights (21), and census-based job information linked to a job-exposure matrix indicating percentage of shift workers for a given job title (22). Also, there is substantial variability in the organization of shift work (e.g., timing of shifts, schedule of days/nights, duration of shifts, number of consecutive shifts), and there is some evidence implying that certain work patterns, such as a greater number of consecutive night shifts, may disrupt circadian

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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**doi:** 10.1158/1055-9965.EPI-18-1112

rhythms more than other parameters (23–25). However, epidemiologic studies have often aggregated shift work patterns differing in timings and schedule into one or two overall measurements (23).

Discrepancies between studies may also be attributed to the lack of consideration of chronotype, that is, an individual's biological preference as a "morning," "intermediate," or "evening" person (26), which is potentially an important effect modifier of the relationship between shift work and cancer. A person's circadian rhythm is synchronized to sleep and wake times through the regulation of physiologic processes such as the production of melatonin, where people with "evening" chronotypes are synchronized to evening time periods (i.e., melatonin production peaks later), and can sleep and wake later with ease, while people with "morning" chronotypes prefer the opposite (27). Research has shown that people with "evening" chronotypes may be more tolerant to shift work (28, 29), which may suggest that the mechanism by which shift work impacts cancer risk may differ across chronotypes. Chronotype has been considered in only one previous ovarian cancer study where the findings suggested an increased risk associated with shift work among those self-identified as "morning" people, with weaker relative risk estimates for "evening" people (19). Another potential effect modifier is menopausal status as supported by a recent combined analysis of breast cancer studies, where shift work was associated with an increased risk among premenopausal women only (30). EOC is a hormone-sensitive cancer and it is hypothesized that shift work may elevate estrogen levels through light at night-induced endocrine dysregulation, and this may be differential by menopausal status.

In a population-based case–control study, we investigated the relationship between shift work exposure and risk of EOC overall, by tumor behavior (invasive, borderline), and separately for high-grade serous carcinoma (HGSC), the most common form of EOC. Associations were also examined according to chronotype and menopausal status.

## Materials and Methods

### Study population

The PRevention of OVArian Cancer in Quebec (PROVAQ) study is a population-based case–control study conducted in Montreal, Canada in 2011–2016 (31). All study participants were women ages 18–79 years who were Canadian citizens, residents of the metropolitan area of Montreal, and able to communicate in French or English. Cases were women newly diagnosed with EOC, including primary peritoneal and fallopian tube cancers, and recruited from seven Montreal hospitals that care for the large majority of women diagnosed with ovarian cancer in Montreal. A total of 652 women with histologically confirmed EOC were eligible and asked to participate, of whom 78% ($n = 507$) gave consent to participate. Nine participants were later excluded as their cancers were nonepithelial or metastatic, leaving 498 cases. Cases were classified by tumor behavior (invasive, borderline) as well as on histology and grade (32). Population controls were identified from the Quebec Electoral List and were frequency-matched to cases on five-year age categories and electoral district. Of 1,634 eligible controls asked to participate, 56% ($n = 908$) agreed to participate. All cases and controls provided written informed consent.

### Data collection

In-person interviews were used to ascertain sociodemographic information, medical history, medication use, reproductive characteristics, anthropometric measurements, other lifestyle factors, and lifetime occupational history including shift work details for each job held. On the basis of the question "Do you consider yourself to be a morning person, more morning than evening, more evening than morning, or an evening person?" participants self-reported their chronotype. Information pertinent to the determination of menopausal status (31) was also collected during the interview. Interviews were conducted an average of 4.8 months after diagnosis for cases. Occupations were classified according to the International Standard Classification of Occupations 1968, by an occupational hygienist, based on job titles and description of tasks.

### Shift work assessment

For each job, volunteer activity, period as a full-time graduate student or period as a homemaker held for at least six months over the age of 19 years until the referent age (age of diagnosis for cases, age of interview for controls), participants reported the job title, duration each job was held, status (part-time, full-time), work pattern [fixed days (6 am–6 pm), fixed evenings (6 pm–12 am), fixed nights (12 am–6 am), rotating (alternating day shifts with night/evening shifts), or other], number of night shifts per month, and number of consecutive night shifts per month. For work patterns reported as "other," participants provided a short statement describing their exact schedule that was later categorized into one of the predefined questionnaire work patterns. Periods reported as a homemaker were considered a fixed day pattern. Eight participants who were students aged 25 and younger at recruitment reported no prior employment and were classified as having a fixed day work pattern from age 19 to their referent age. Two controls and two cases were excluded due to incomplete occupational history, leaving 496 cases and 906 controls for analysis.

The IARC Monographs defined shift work as "any arrangement of daily working hours other than the standard daylight hours of 7/8 am–5/6 pm" (4), which encompasses work patterns of fixed evenings, fixed nights, and rotating (with either evening shifts or night shifts). We defined three shift work exposure variables: cumulative years of shift work exposure, average number of night shifts per month, and average number of consecutive night shifts per month. Cumulative years of exposure was calculated for any shift work as well as for individual shift work patterns defined on the basis of shift times (ever night shift work, evening shift work only) and schedules (rotating shift work only, fixed shift work only; Fig. 1). The ever night shift work exposure group included participants exposed to night shifts only as well as to both evening and night shifts. We were unable to include a group restricted to participants exposed to night shifts only due to a small number of exposed participants. Cumulative years of shift work exposure were calculated as in Eq. (A):

$$C = \sum_{i=1}^{n} (D_i \times F_i) \quad \text{(A)}$$

where C is lifetime cumulative years of exposure, $n$ refers to the total number of jobs with shift work across a participant's lifetime, $i$ refers to a specific job with shift work, $D$ is job duration in years, and $F$ is part-time or full-time equivalency (0.5 for part-time, 1.0 for full-time). The variable for cumulative years of exposure to any shift work was categorized into tertiles based on shift working

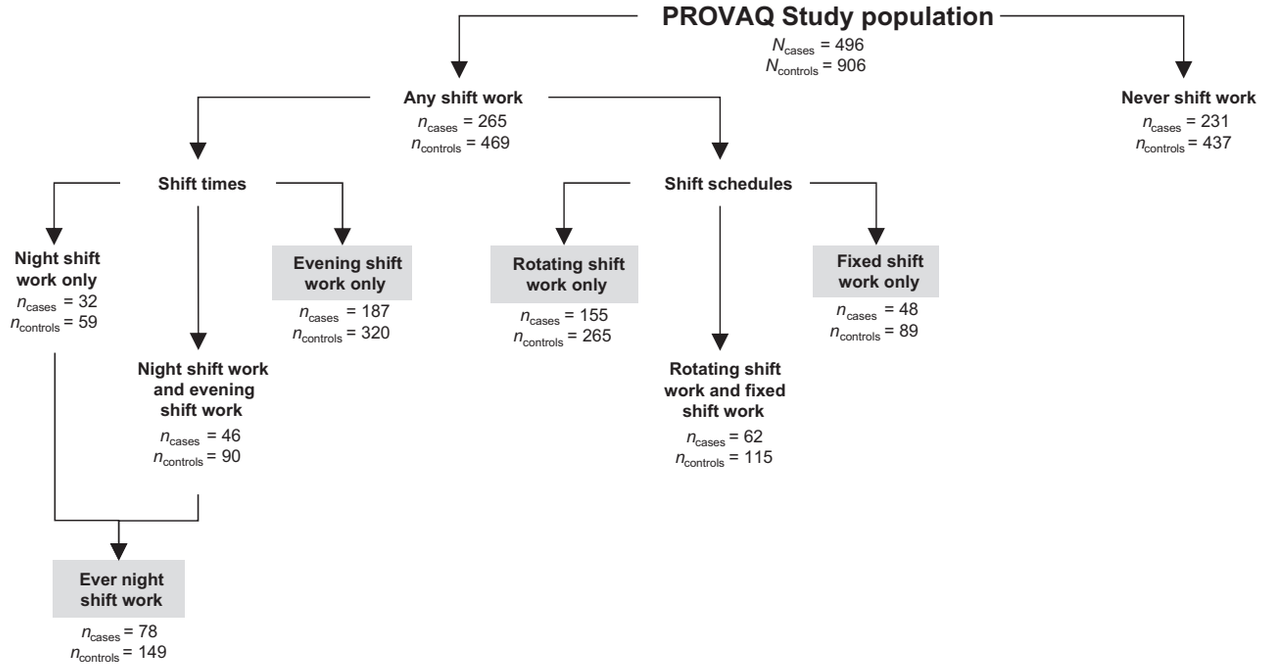


**Figure 1.**

Shift work exposure assessment and deconstruction of the any shift work exposure variable into individual shift work patterns (shaded) included in the analysis: ever night shift work, evening shift work only, rotating shift work only, and fixed shift work only.

controls; for individual shift work patterns, cumulative years of exposure was dichotomized on the basis of the median among shift working controls. For participants exposed to night shifts, the number of night shifts per month was determined by taking an average of the number of night shifts per month from all positions involving night shifts. For the analysis, exposure categories were created by dichotomizing at the median among ever night shift working controls. The exposure categories for the variable for average number of consecutive night shifts per month were produced using the same method. Because the question on the number of consecutive night shifts was added after the study began, ever night shift workers who were never asked the question were excluded from the analysis of these variables (15 cases, 25 controls).

### Statistical analysis

Multivariable unconditional logistic regression was used to estimate ORs and 95% confidence intervals (CIs) for the associations between overall EOC risk and each shift work exposure variable, with women without shift work experience (i.e., never shift workers) as the reference group. Confounders of the shift work and EOC association were identified using directed acyclic graphs (DAG) combined with change-in-estimate procedures (33). Potential confounders that were considered are indicated in our DAG (Supplementary Fig. S1) and included age, ethnicity, family history of ovarian cancer, education level, BMI, parity, breastfeeding duration, duration of oral contraceptive use, history of tubal ligation, hormone replacement therapy use, endometriosis, medically diagnosed infertility and smoking history. From these variables, we identified a minimally sufficient confounder set, which all models were adjusted for, that included age (continuous), education (<high school, high school, college/technical, University undergraduate, University graduate), and parity (nulliparous, 1, 2, $\geq$3 full-term births). In the last step of this confounder selection method, each variable not included in the minimally sufficient confounder set was reevaluated (33); no other variable was identified as a confounder. $P_{trend}$ across exposure categories was calculated by considering the category ranks as a continuous variable in the logistic regression model and evaluating the Wald $\chi^2$ test statistic with one degree of freedom to test for a linear effect on the logit of the probability of EOC or EOC subgroup.

Multivariable polytomous logistic regression was used to estimate ORs and 95% CIs for the associations according to tumor behavior (i.e., invasive and borderline). Heterogeneity in the associations by tumor behavior was tested using likelihood ratio tests that compared a model where ORs were constrained to be equal among subgroups, to a model where ORs were allowed to differ between subgroups (34). We evaluated whether ORs for shift work and overall EOC risk were modified by chronotype (morning, intermediate, evening) and by menopausal status (premenopausal, postmenopausal) by including product terms for shift work and the effect modifier of interest. These analyses were conducted for cumulative years of exposure to any shift work, as well as for cumulative years of exposure to evening shift work only and rotating shift work only; sample sizes were too small for ever night shift work and fixed night shift work only. *P* values for multiplicative interaction were produced using likelihood ratio tests comparing the regression models with and without the product terms.

In three separate sensitivity analyses to examine the possible influence of reverse-causality bias and/or a lagged effect of shift work given the possible induction period of ovarian cancer, occupational history 2, 5, and 10 years prior to referent age were excluded from the cumulative years of exposure variable for cases

and controls. Two sensitivity analyses addressing the categorization of shift work were conducted where the variable for any shift work exposure was dichotomized (ever, never) and categorized using cutoffs from studies of breast cancer (<15, 15–29, >29 years). All statistical analyses were conducted using SAS software version 9.4 (SAS Institute).

## Results

Table 1 describes the study population according to all variables considered in this analysis. Cases and controls had similar distributions according to age group and ethnicity, and small differences for other characteristics, except that a greater proportion of controls had one or more children and a longer duration of oral contraceptive use. Among EOC subgroups, invasive cases were more likely to be postmenopausal and have a family history of ovarian or breast cancer compared with controls, while borderline cases were younger and more likely to be premenopausal, less educated, and have more pack-years of smoking compared with controls.

Just over half of both cases and controls participated in any shift work, and similar distributions were observed for cases and controls for participation in individual shift work patterns (Fig. 1). Table 2 shows the main occupations in which shift work was recorded. Medical, dental, veterinary, and related workers (13.0% of all shift workers); cooks, waiters, bartenders, and related workers (10.2%); and bookkeepers, cashiers, and related workers (9.4%) were the top three shift work occupations. When examined according to shift times and schedules, professional nurses were common across any shift times/schedules, and particularly for fixed night shifts. Among fixed evening shifts, "authors, journalists, and related writers" was the most common occupation group and among rotating shifts, "salespeople, shop assistants, and sales demonstrators" was the most common occupation group.

Table 3 displays associations for cumulative years of shift work with overall EOC risk as well as risk by tumor behavior. For EOC overall, the OR (95% CI) for the highest category of cumulative years of exposure to any shift work (i.e., > 12 years) versus never exposed to shift work was 1.21 (0.89–1.63); however, a monotonic dose–response relationship pattern was not observed. Similarly, no strong pattern of association was observed for shift work variables defined according to shift times and schedules (Table 3). These adjusted ORs did not appreciably differ when occupational history for 2, 5, and 10 years prior to referent date was excluded (results not shown). When never shift workers were removed and the lowest shift work category was used as a reference, the ORs reflected the same pattern of associations seen in Table 2 (results not shown). When cumulative years of exposure to any shift work was categorized as ever versus never shift work, the adjusted OR (95% CI) for overall EOC risk was 1.00 (0.99–1.01). When categorized using cutoffs from breast cancer studies, the adjusted ORs (95% CI), compared with never shift work, were 0.96 (0.75–1.23) for <15 years, 1.26 (0.87–1.82) for 15–29 years, and 1.20 (0.72–2.01) for >29 years. When we restricted the analysis to women who have held at least one job outside of the home, to address the fact that workers may be generally healthier, the ORs were virtually unchanged (results not shown). Associations for invasive and borderline tumors separately did not appreciably differ from each other, nor from what was seen for all EOCs combined (Table 3). When cases were restricted to HGSC, the adjusted ORs (95 CI %), compared with never shift work, were 1.29 (0.86–1.94) for <5 years versus never shift work, 0.75 (0.48–1.17) for 5–12 years versus never shift work, and 1.40 (0.97–2.04) for >12 years.

When focusing on night shift work, the observed ORs did not significantly differ from the null value for different levels of both average number of night shifts per month and average number of consecutive night shifts per month, both compared with never shift workers (Table 4). When examined according to chronotype, a positive association between shift work and EOC overall was observed among women identified as having "morning" chronotypes, which was statistically significant for the highest category of cumulative years of any shift work, while among women identified as having "evening" chronotypes an inverse association was observed, also statistically significant for the highest category of cumulative years of any shift work (Table 5); however, this difference in ORs for women with "morning" versus "evening" chronotypes was not statistically significant. Inverse associations for the highest cumulative shift work years versus never among women with "evening" chronotypes were also suggested for the shift patterns of evening shift work only (OR = 0.63; 95% CI: 0.40–1.52) and rotating shift work only (OR = 0.67; 95% CI: 0.26–1.77). Associations between cumulative years of any shift work and EOC risk did not significantly vary between premenopausal and postmenopausal women (Table 5).

## Discussion

In this population-based case–control study, we did not observe evidence of an association between cumulative years of shift work, defined as any shift work as well as according to shift times (ever night shift work, evening shift work only) and schedules (rotating shift work only, fixed shift work only), and overall EOC risk. Associations for invasive and borderline EOC were similar to that observed for EOC overall. The OR for the highest level of any shift work and HGSC suggested a marginally significant increased risk, but as for the associations of EOC overall and for invasive and borderline cancers separately, the ORs across categories were nonmonotonic. When associations were examined according to chronotype or menopausal status, we did not observe statistically significant differences in associations between cumulative years of shift work and risk of EOC overall. Nonetheless, there was some suggestion that a positive association was specific to women with a "morning" chronotype while among women with an "evening" chronotype, shift work was associated with a reduced EOC risk.

To date, four studies have investigated the specific relationship between shift work and EOC risk (18). A null association was reported in a retrospective cohort study with exposure defined according to census reported job titles linked to a job-exposure matrix defining the percentage of shift workers in each job title (22). Similarly, there was no strong evidence of an association in a prospective cohort study of rotating shift work with night shifts among nurses (21), while in another cohort study a positive association was observed between current rotating work at baseline and fatal ovarian cancer (20). Most similar to ours is the population-based case–control study by Bhatti and colleagues (19) that based exposure on an assessment of lifetime occupational history and enrolled women in similar calendar years. In that study, ever night shift work was associated with increased risks of invasive and borderline EOCs (19). However,

**Table 1.** Characteristics of PROVAQ study participants, *n* (%)

| | Controls (*N* = 906) | Full case group (*N* = 496) | Invasive cases (*n* = 362) | Borderline cases (*n* = 134) |
|---|---|---|---|---|
| Age (years) | | | | |
| <45 | 116 (12.8) | 63 (12.7) | 26 (7.2) | 37 (27.6) |
| 45 to <55 | 212 (23.4) | 129 (26.0) | 97 (26.8) | 32 (23.9) |
| 55 to <65 | 294 (32.5) | 162 (32.7) | 122 (33.7) | 40 (29.9) |
| ≥65 | 284 (31.3) | 142 (28.7) | 117 (32.3) | 25 (18.7) |
| Menopausal status[a,b] | | | | |
| Premenopausal | 291 (32.1) | 161 (32.5) | 105 (29.7) | 56 (41.8) |
| Postmenopausal | 589 (65.0) | 323 (65.1) | 249 (70.3) | 74 (55.2) |
| Self-reported ethnicity[a] | | | | |
| French Canadian | 607 (67.0) | 337 (68.1) | 244 (67.6) | 93 (69.4) |
| Other European ancestry | 216 (23.9) | 115 (23.2) | 85 (23.5) | 30 (22.4) |
| Other/mixed ancestry | 82 (9.1) | 43 (8.7) | 32 (8.9) | 11 (8.2) |
| Family history of cancer in first-degree female relatives[a] | | | | |
| Ovarian | 22 (2.4) | 26 (5.2) | 22 (6.1) | 4 (3.0) |
| Breast | 146 (16.1) | 89 (17.9) | 77 (21.3) | 12 (9.0) |
| Education level | | | | |
| ≤High school | 281 (31.0) | 191 (38.5) | 134 (37.0) | 57 (42.5) |
| College/technical | 277 (30.6) | 144 (29.0) | 107 (29.6) | 37 (27.6) |
| ≥University, undergraduate | 348 (38.4) | 161 (32.5) | 121 (33.4) | 40 (29.9) |
| BMI (kg/m$^2$) | | | | |
| <18.5 | 36 (4.0) | 25 (5.0) | 17 (4.7) | 8 (6.0) |
| 18.5 to <25 | 423 (46.7) | 218 (44.0) | 161 (44.5) | 57 (42.5) |
| 25 to <30 | 277 (30.5) | 139 (28.0) | 100 (27.6) | 39 (29.1) |
| ≥30 | 170 (18.8) | 114 (23.0) | 84 (23.2) | 30 (22.4) |
| Parity (full-term births) | | | | |
| Nulliparous | 197 (21.8) | 166 (33.5) | 114 (31.5) | 52 (38.8) |
| 1 | 160 (17.7) | 102 (20.6) | 77 (21.3) | 25 (18.7) |
| 2 | 354 (39.1) | 156 (31.4) | 115 (31.8) | 41 (30.6) |
| ≥3 | 194 (21.4) | 72 (14.5) | 56 (15.5) | 16 (11.9) |
| Breastfeeding duration (months) | | | | |
| Never | 475 (52.4) | 323 (65.1) | 234 (64.7) | 89 (66.4) |
| 0 to <6 | 184 (20.3) | 88 (17.7) | 66 (18.2) | 22 (16.4) |
| ≥6 | 247 (27.3) | 85 (17.2) | 62 (17.1) | 23 (17.2) |
| Oral contraceptive use (years)[a] | | | | |
| Never | 172 (19.0) | 107 (21.7) | 90 (24.9) | 17 (12.9) |
| 0 to <2 | 158 (17.4) | 94 (19.0) | 65 (18.0) | 29 (22.0) |
| 2 to <10 | 334 (36.9) | 195 (39.5) | 146 (40.3) | 49 (37.1) |
| ≥10 | 242 (26.7) | 98 (19.8) | 61 (16.9) | 37 (28.0) |
| History of tubal ligation | | | | |
| Never | 662 (73.1) | 387 (78.0) | 272 (75.1) | 115 (85.8) |
| Ever | 244 (26.9) | 109 (22.0) | 90 (24.9) | 19 (14.2) |
| Hormone replacement therapy use[a] | | | | |
| Never | 619 (69.2) | 325 (66.1) | 228 (63.5) | 97 (72.9) |
| Ever | 276 (30.8) | 167 (33.9) | 131 (36.5) | 36 (27.1) |
| Endometriosis[c] | | | | |
| Never | 838 (94.2) | 424 (87.2) | 310 (87.1) | 114 (87.7) |
| Ever | 52 (5.8) | 62 (12.8) | 46 (12.9) | 16 (12.3) |
| Medically diagnosed infertility | | | | |
| Never | 856 (94.5) | 459 (92.5) | 333 (92.0) | 126 (94.0) |
| Ever | 50 (5.5) | 37 (7.5) | 29 (8.0) | 8 (6.0) |
| Smoking history (pack-years)[a] | | | | |
| Never | 423 (47.1) | 197 (41.0) | 155 (43.9) | 42 (33.1) |
| 0 to <25 | 304 (33.8) | 189 (39.4) | 140 (39.7) | 49 (38.6) |
| ≥25 | 172 (19.1) | 94 (19.6) | 58 (16.4) | 36 (28.3) |
| Chronotype[a] | | | | |
| Morning | 379 (41.8) | 203 (41.0) | 156 (43.2) | 47 (35.1) |
| Intermediate | 367 (40.5) | 214 (43.2) | 152 (42.1) | 62 (46.3) |
| Evening | 160 (17.7) | 78 (15.8) | 53 (14.7) | 25 (18.6) |

[a]Missing information: family history of cancer (25 controls, 8 cases), self-reported ethnicity (1 control, 1 case), oral contraceptive use (2 cases), smoking history (7 controls, 16 cases), and chronotype (1 case).
[b]Menopausal status was unknown for 26 controls and 12 cases (8 invasive cases, 4 borderline cases).
[c]Endometriosis history unknown for 16 controls and 10 cases (6 invasive cases, 4 borderline cases).

cumulative years of night shift work were not associated with a monotonic dose–response relationship; in particular, relative risks increased with increasing cumulative years except for the highest category where the association was attenuated and null (19). Our results also suggested a nonmonotonic relationship, but the shape was different, with the OR for the highest

**Table 2.** Most common shift work occupations in the PROVAQ study population, classified according to the International Standard Classification of Occupations 1968 (ISCO-68), *n* (%)

| Occupations[a] | Any shift work (*n* = 1,663) | Fixed night shift (*n* = 108) | Fixed evening shift (*n* = 381) | Rotating shift (*n* = 1,174) |
|---|---|---|---|---|
| Medical, dental, veterinary, and related workers[b] | 217 (13.0) | 34 (31.5) | 57 (15.0) | 126 (10.7) |
| Professional nurses[c] | 169 (10.2) | 30 (27.8) | 44 (11.5) | 95 (8.1) |
| Medical doctors[c] | 27 (1.6) | — | — | 27 (2.3) |
| Cooks, waiters, bartenders, and related workers[b] | 156 (9.4) | 22 (20.4) | 46 (12.1) | 88 (7.5) |
| Bookkeepers, cashiers, and related workers[b] | 151 (9.1) | 5 (4.6) | 34 (8.9) | 112 (9.5) |
| Salespeople, shop assistants, and related workers[b] | 142 (8.5) | <5 | 12 (3.1) | 129 (11.0) |
| Authors, journalists, and related writers[b] | 123 (7.4) | <5 | 63 (16.5) | 59 (5.0) |
| All other occupations[b] | 874 (52.6) | 45 (41.7) | 169 (44.4) | 660 (56.2) |

[a]Only occupations with a valid ISCO-68 occupation code were included.
[b]Occupation grouping based on 2 digits of ISCO-68.
[c]Occupation grouping based on 3 digits of ISCO-68.

category in our study suggesting a positive association. The study by Bhatti and colleagues (19) included night shift work only, while ours included all shift work types. Also, our sample size was smaller precluding an analysis of long-term shift work; in fact, our highest category of cumulative years was included within their second highest category where they observed an increased risk (19).

The study by Bhatti and colleagues (19) was also the only other study that examined modification of associations by chronotype and reported a positive association between shift work and ovarian cancer among women self-identified as having a "morning" chronotype but not an "evening" chronotype (19). We also observed a positive association among women with a "morning" chronotype, but we further observed an inverse association between shift work and EOC among women with an "evening" chronotype. Given the relatively small numbers of women in each chronotype strata, this may be a chance finding. However, night shift workers were included in our study population and this observation is coherent with the hypothesis that people with circadian rhythms synchronized to be more active in the evening, such that melatonin peaks later, may adapt better to shift work hours. Chronotype has been observed to modify

**Table 3.** Multivariable ORs (95% CIs) for the relationship between cumulative years of exposure to any shift work and four shift work patterns and overall, invasive, and borderline EOC

| Cumulative years of shift work | Controls (*N* = 906) *n* (%)[a] | All cases (*N* = 496) *n* (%)[a] | All cases (*N* = 496) OR[b] (95% CI) | Invasive cases (*n* = 362) *n* (%)[a] | Invasive cases (*n* = 362) OR[b] (95% CI) | Borderline cases (*n* = 134) *n* (%)[a] | Borderline cases (*n* = 134) OR[b] (95% CI) | $P_{het}$[c] |
|---|---|---|---|---|---|---|---|---|
| Any shift work | | | | | | | | |
| Never | 437 (48.3) | 231 (46.6) | 1.00 (ref) | 171 (47.2) | 1.00 (ref) | 60 (44.8) | 1.00 (ref) | 0.65 |
| <5 | 146 (16.1) | 93 (18.8) | 1.21 (0.88–1.67) | 66 (18.2) | 1.22 (0.86–1.73) | 27 (20.1) | 1.19 (0.71–1.98) | |
| 5–12 | 168 (18.5) | 67 (13.5) | 0.74 (0.53–1.03) | 44 (12.2) | 0.67 (0.46–0.99) | 23 (17.2) | 0.92 (0.54–1.56) | |
| >12 | 155 (17.1) | 105 (21.2) | 1.21 (0.89–1.63) | 81 (22.4) | 1.25 (0.90–1.74) | 24 (17.9) | 1.10 (0.65–1.86) | |
| $P_{trend}$[d] | | | 0.75 | | 0.72 | | 0.88 | |
| Ever night shift work | | | | | | | | |
| Never | 437 (74.6) | 231 (74.8) | 1.00 (ref) | 171 (75.3) | 1.00 (ref) | 60 (73.2) | 1.00 (ref) | 0.48 |
| <5.5 | 73 (12.4) | 40 (12.9) | 1.07 (0.70–1.64) | 31 (13.7) | 1.14 (0.71–1.83) | 9 (11.0) | 0.85 (0.39–1.84) | |
| ≥5.5 | 76 (13.0) | 38 (12.3) | 0.88 (0.58–1.36) | 25 (11.0) | 0.80 (0.50–1.32) | 13 (15.9) | 1.12 (0.58–2.18) | |
| $P_{trend}$[d] | | | 0.69 | | 0.56 | | 0.85 | |
| Evening shift work only | | | | | | | | |
| Never | 437 (57.7) | 231 (55.3) | 1.00 (ref) | 171 (55.9) | 1.00 (ref) | 60 (53.6) | 1.00 (ref) | 0.96 |
| <3 | 122 (16.1) | 82 (19.6) | 1.27 (0.92–1.77) | 56 (18.3) | 1.25 (0.86–1.80) | 26 (23.2) | 1.33 (0.79–2.25) | |
| ≥3 | 198 (26.2) | 105 (25.1) | 0.98 (0.73–1.31) | 79 (25.8) | 0.98 (0.72–1.36) | 26 (23.2) | 0.96 (0.58–1.58) | |
| $P_{trend}$[d] | | | 0.92 | | 0.92 | | 0.97 | |
| Rotating shift work only | | | | | | | | |
| Never | 437 (62.2) | 231 (59.8) | 1.00 (ref) | 171 (59.8) | 1.00 (ref) | 60 (60.0) | 1.00 (ref) | 0.38 |
| <3.5 | 132 (18.8) | 77 (19.9) | 1.12 (0.81–1.56) | 60 (21.0) | 1.23 (0.85–1.76) | 17 (17.0) | 0.86 (0.48–1.56) | |
| ≥3.5 | 133 (19.0) | 78 (20.2) | 1.06 (0.76–1.47) | 55 (19.2) | 1.01 (0.70–1.45) | 23 (23.0) | 1.19 (0.70–2.02) | |
| $P_{trend}$[d] | | | 0.64 | | 0.75 | | 0.64 | |
| Fixed shift work only | | | | | | | | |
| Never | 437 (83.1) | 231 (82.8) | 1.00 (ref) | 171 (83.4) | 1.00 (ref) | 60 (81.1) | 1.00 (ref) | 0.49 |
| <3 | 31 (5.9) | 25 (9.0) | 1.50 (0.86–2.63) | 19 (9.3) | 1.63 (0.89–2.98) | 6 (8.1) | 1.19 (0.46–3.04) | |
| ≥3 | 58 (11.0) | 23 (8.2) | 0.73 (0.44–1.23) | 15 (7.3) | 0.64 (0.35–1.17) | 8 (10.8) | 1.01 (0.45–2.27) | |
| $P_{trend}$[d] | | | 0.53 | | 0.41 | | 0.90 | |

[a]Percentages are based on total number of participants for each shift work exposure group.
[b]Adjusted for age (continuous), education (<high school, high school, college/technical, university undergraduate, university graduate), and parity (nulliparous, 1, 2, ≥3 full-term births).
[c]*P* value for heterogeneity between invasive and borderline EOCs.
[d]*P* value for trend across cumulative years of exposure categories.

**Table 4.** Multivariable ORs (95% CIs) for the relationship between the average number of night shifts per month and overall EOC risk, and the average number of consecutive night shifts per month and overall EOC risk, among ever night shift workers

| Exposure metrics | Cases ($N = 309$) *n* (%) | Controls ($N = 586$) *n* (%) | OR[a] (95% CI) |
|---|---|---|---|
| Average number of night shifts per month[b] | | | |
| Never | 231 (75.3) | 437 (75.3) | 1.00 (ref) |
| <12 nights per month | 33 (10.7) | 70 (12.1) | 0.91 (0.58–1.43) |
| ≥12 nights per month | 43 (14.0) | 73 (12.6) | 1.06 (0.70–1.61) |
| Average number of consecutive night shifts per month[c] | | | |
| Never | 231 (79.3) | 437 (79.0) | 1.00 (ref) |
| <4 consecutive nights | 26 (8.9) | 60 (10.8) | 0.92 (0.55–1.53) |
| ≥4 consecutive nights | 34 (11.6) | 56 (10.2) | 1.24 (0.77–2.00) |

[a]Adjusted for age (continuous), education (<high school, high school, college/technical, university undergraduate, university graduate), and parity (nulliparous, 1, 2, ≥3 full-term births).
[b]Two cases and 6 controls had missing data for the average number of night shifts per month.
[c]Fifteen cases and 25 controls were excluded from this analysis, as the question on number of consecutive night shifts per month was added after their study participation; a further 3 cases and 8 controls had missing data for this variable.

associations for shift work with other hormone-sensitive cancers (i.e., breast and prostate cancers; refs. 35–37). The investigation of menopausal status as a potential effect modifier allowed us to examine whether different hormone profiles may differentially affect exposure to shift work in association with ovarian cancer. Similar to the only other ovarian cancer study that examined associations by menopausal status (21), we observed that ORs did not vary according to menopausal status.

The collection of detailed shift information for each job held by participants enabled the analysis of individual shift work patterns defined according to shift times and schedules. Although we did not observe evidence of associations, these analyses allowed us to address the hypothesis that different shift work patterns may contribute to varying degrees of circadian disruption (23, 24). The frequency and intensity of night shift work have only been analyzed for breast cancer risk, where two studies reported that night shift workers working more frequent and intense schedules have increased risks (35, 38). Our study included a small number of night shift workers with a high frequency or high intensity of night shifts, thus the OR estimates for these analyses were imprecise.

Despite the inclusion of almost 500 cases and the fact that a large proportion of the PROVAQ study population was exposed to shift work, relatively small numbers were exposed to long-term shift work. Thus, if an association exists for long-term shift work (e.g., >25 years) as seen in some breast cancer studies (30), we would not have been able to detect this. We believe that if there were errors in recounting shift work history, this would likely have affected cases and controls equally as participants were not directly asked to report their previous shift work, rather they were asked about several job details, including work patterns involving shifts, after they had first listed all jobs in their history with the aid of a life events calendar. According to one study, in comparison with individual payroll data, the reporting of shift work experiences with night shifts demonstrated high sensitivity (>90%) and specificity (>92%), and questions on shift work experiences without night shifts showed low sensitivity (62%) and moderate specificity (87%; ref. 39). Chronotype may have been misclassified in our study due to self-report, compared with other studies that utilized tools such as the Munich ChronoType Questionnaire (40), which takes into account temporal preferences on work and nonwork days, specific sleep and activity times, and outdoor light exposure in the determination of an individual's chronotype. However, the degree of misclassification may be minimal as one study has demonstrated that self-reported chronotype is highly correlated to the determination of chronotype using a validated questionnaire (41). Furthermore, our results suggest that associations varied by chronotype in a direction consistent with the hypothesis that women with "evening" chronotypes may be better adapted to shift work hours compared with women with "morning" chronotypes.

**Table 5.** Multivariable ORs (95% CIs) for the relationship between cumulative years of exposure to any shift work and overall risk of ovarian cancer, by chronotype and menopausal status

| | Cumulative years of exposure to any shift work | | | | *P* | |
|---|---|---|---|---|---|---|
| | Never | <5 | 5–12 | >12 | Trend[a] | Interaction[b] |
| By chronotype | | | | | | |
| Morning type | | | | | | 0.29 |
| #cases/#controls | 101/207 | 36/55 | 24/66 | 42/51 | | |
| OR[c] (95% CI) | 1.00 (ref) | 1.43 (0.87–2.34) | 0.82 (0.48–1.39) | 1.64 (1.01–2.65) | 0.16 | |
| Intermediate type[d] | | | | | | |
| #cases/#controls | 99/190 | 44/70 | 36/75 | 43/62 | | |
| OR[c] (95% CI) | 1.00 (ref) | 0.82 (0.42–1.61) | 1.04 (0.52–2.11) | 0.74 (0.38–1.45) | 0.47 | |
| Evening type | | | | | | |
| #cases/#controls | 30/40 | 13/21 | 7/27 | 20/42 | | |
| OR[c] (95% CI) | 1.00 (ref) | 0.56 (0.21–1.51) | 0.36 (0.12–1.10) | 0.37 (0.15–0.88) | 0.02 | |
| By menopausal status | | | | | | |
| Premenopausal | | | | | | 0.67 |
| #cases/#controls | 67/129 | 45/62 | 25/67 | 24/33 | | |
| OR[c] (95% CI) | 1.00 (ref) | 1.45 (0.89–2.39) | 0.67 (0.38–1.16) | 1.32 (0.71–2.45) | 0.97 | |
| Postmenopausal | | | | | | |
| #cases/#controls | 161/294 | 46/81 | 38/96 | 78/118 | | |
| OR[c] (95% CI) | 1.00 (ref) | 0.71 (0.37–1.35) | 0.12 (0.55–2.25) | 0.87 (0.43–1.76) | 0.80 | |

[a]$P_{trend}$ across cumulative years of exposure categories.
[b]$P_{interaction}$ using the likelihood ratio test to compare regression models with and without interaction terms.
[c]Adjusted for age (continuous), education (<high school, high school, college/technical, university undergraduate, university graduate), and parity (nulliparous, 1, 2, ≥3 full-term births).
[d]Intermediate chronotype combined women reporting that they were "more morning than evening" or "more evening than morning" people.

Because the participation rate among controls was 56% and information collected from eligible nonparticipating controls indicated they were older and had a lower level of education (31), participating controls may not have accurately represented the study base with respect to shift work prevalence. In particular, education level is associated with shift work participation, as shift work is more common in occupations that provide services 24 hours per day, such as healthcare and social assistance, retail trades, and accommodation and food services (42). The adjustment for education level in our analyses reduced the impact of potential selection bias due to differential participation according to education level (43). Although we considered a variety of confounders in our directed acyclic graphs, uncontrolled confounding from unknown factors related to shift work participation cannot be ruled out.

In summary, this study does not support an overall association between shift work exposure and EOC risk. However, our results suggest that chronotype should be considered in studies of shift work as an exposure. As shift work is a prevalent exposure that is a probable human carcinogen, the examination of the organization of shift work, such as according to shift times and schedules, may lead to an increased understanding of the role on cancer risk.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Authors' Contributions

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## Acknowledgments

This research was supported by the Canadian Cancer Society (grant no. 700485) and the Cancer Research Society, the Fonds de recherche du Québec-Santé and the Ministère de l'Économie, de la Science et de l'Innovation du Québec GRePEC program (grant no. 16264). A. Koushik was supported by the Cancer Research Society-Cancer Guzzo Université de Montréal Award, the Fonds de recherche du Québec-Santé Research Scholar Program, and the Canadian Institutes of Health Research New Investigator program. J. Siemiatycki holds the Guzzo-Cancer Research Society Chair in Environment and Cancer. We are grateful to our study coordinator Julie Lacaille; to our interviewers Claire Walker, Françoise Pineault, and Martine Le Comte; to Dora Rodriguez for coding jobs; and to Ana Gueorguieva for data management.

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Received October 13, 2018; revised December 3, 2018; accepted February 26, 2019; published first March 6, 2019.

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