Published in final edited form as:
Occup Environ Med. 2013 April ; 70(4): 231–237. doi:10.1136/oemed-2012-101146.

Nightshift work and risk of ovarian cancer

Parveen Bhatti[1], **Kara L. Cushing-Haugen**[1], **Kristine G. Wicklund**[1], **Jennifer A. Doherty**[1,2], and **Mary Anne Rossing**[1]

[1]Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[2]Section of Biostatistics and Epidemiology, The Geisel School of Medicine at Dartmouth, Lebanon, NH, USA

Abstract

Objectives—Animal evidence suggests that circadian disruption may be associated with ovarian cancer, though very little epidemiologic work has been done to assess this potential association. We evaluated the association between self-reported nightshift work, a known circadian disruptor, and ovarian cancer in a population-based case-control study.

Methods—The study included 1,101 women with invasive epithelial ovarian cancer, 389 women with borderline epithelial ovarian tumors and 1,832 controls and was conducted in Western Washington State. Shift work data was collected as part of in-person interviews.

Results—Working the nightshift was associated with an increased risk of invasive (OR=1.24, 95% CI: 1.04–1.49) and borderline (OR=1.48, 95% CI: 1.15–1.90) tumors; however, we observed little evidence that risks increased with increasing cumulative duration of nightshift work, and risks were not elevated in the highest duration category (>7 nightshift work-years). Increased risks were restricted to women who were 50 years of age and older and to serous and mucinous histologies of invasive and borderline tumors. There was suggestive evidence of a decreased risk of ovarian cancer among women reporting a preference for activity during evenings rather than mornings.

Conclusion—We found evidence suggesting an association between shift work and ovarian cancer. This observation should be followed up in future studies incorporating detailed assessments of diurnal preference (i.e. chronotype) in addition to detailed data on shift schedules.

Keywords

shift work; ovarian cancer; circadian; chronotype

Correspondence and reprint requests to: Parveen Bhatti, Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, P.O. Box 19024 M4-B874, Seattle, WA 98109, TEL: 206-667-7803, FAX: 206-667-4787, pbhatti@fhcrc.org.

Competing Interests
None to report.

Introduction

It is estimated that over 22,000 new cases of ovarian cancer will be diagnosed in the United States in 2012, with over 15,000 deaths from the disease [1]. There are few known factors that influence risk of ovarian cancer, including hormonal contraceptive use, parity and heavier body weight [2]. Given the high mortality rate among patients with ovarian cancer, the identification of potentially modifiable risk factors is crucial to disease prevention efforts.

Shift work resulting in circadian disruption has been classified as a probable human carcinogen by the International Agency for Research on Cancer (IARC) [3]. Though the mechanisms behind the carcinogenicity of shift work are not fully understood, they are thought to be mediated by the indoleamine melatonin, which is produced at nighttime and suppressed by ambient light [4]. Melatonin is a regulator of the hypothalamic-pituitary-gonadal axis, and the effect of melatonin on reproductive hormones, including estrogen, has been considered a primary mechanism by which shift work may be associated with breast cancer risk [5].

This mechanism may also extend to ovarian cancer for which there is evidence that endogenous reproductive hormones are involved in the pathogenesis of the disease [6]. Evidence suggests that melatonin may be directly involved in ovarian function, including follicular development, ovulation, oocyte maturation and luteal function [7]. Extensive animal and cellular experimental data have shown melatonin to have direct oncostatic properties which may be mediated through an effect on reactive oxygen species [8]. In fact, in a study of rats, oral administration of melatonin was shown to decrease lipid hydroperoxide levels, increase total levels of antioxidant substances and increase the activity of antioxidant enzymes, including superoxide dismutase, catalase and glutathione-reductase in ovarian tissue [9].

Despite this suggestive experimental evidence, few epidemiologic studies have examined the association between shift work and ovarian cancer. Here we describe a large population-based case-control study in which we examined the relation of lifetime nightshift work with risk of epithelial ovarian tumors.

Materials and Methods

Study population

Female residents of a thirteen-county area of western Washington State who were diagnosed with a primary invasive or borderline epithelial ovarian tumor from 2002 through 2009 were considered eligible as cases. From 2002–2005, women aged 35–74 years were included, while from 2006–2009 only women aged 35–69 were included. The cases were identified through a population-based cancer registry, the Cancer Surveillance System (CSS), which is part of the Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute. The methods for case ascertainment and for case and control recruitment for 2002–2005 have been previously described [10]; similar methods were used for 2006–2009 [11]. After excluding 61 cases because of a potential language barrier, 2,025 eligible cases were identified, and 1,502 (74.2%) were interviewed. Of the interviewed cases, 1,108 had invasive disease and 394 had borderline tumors. Histologic type was collected and coded by the CSS using the International Classification of Diseases for Oncology (ICD-O) [12] morphology codes and grouped according to the guidelines of the WHO [13] as serous, mucinous, endometrioid, clear cell and other epithelial tumors (comprised largely of unspecified adenocarcinoma and carcinoma). Tumor grade was also collected by the CSS, as grades 1 (well-differentiated) through 4 (undifferentiated) or

unknown. In addition to assessing risk of invasive and borderline tumors separately, we created the following additional analytic groupings of invasive cancers, based on a recent conceptualization of ovarian cancer pathogenesis [14,15]: high-grade serous (HGSC; comprised of serous morphology, grades 2–4 or unknown, as well as grade 3 or higher tumors that were morphologically classified as endometrioid; n=840), low-grade serous (LGSC; grade 1 serous; n=23); mucinous (MC; n=32); endometrioid (EC; morphologically endometrioid and grade 1, 2 or unknown; n=129); and clear cell tumors (CCC; n=84). Based on molecular similarities observed between 1) borderline serous tumors and invasive LGSC, and 2) borderline and invasive mucinous tumors, we further combined invasive and borderline tumors of these subtypes. Other borderline tumors (n=23) were excluded from the subtype analyses.

Controls were selected by random-digit-dialing (RDD) using stratified sampling in 5-year age categories, 1-year calendar intervals and two county strata. From 2002–2005, a 2:1 ratio of controls to women with invasive ovarian cancer was selected using the Waksberg-Mitofsky RDD method [16]. From 2006–2009, a 1:1 ratio of controls to women with invasive disease was used; list-assisted RDD [17] was employed during 2006–2007 and Waksberg-Mitofsky methods during 2008–2009. In total, for 19,092 (78.2%) of the 24,400 telephone numbers belonging to residences, we determined whether an eligible woman (i.e., an age and county eligible woman able to communicate in English and, if so, with at least one ovary and no prior history of ovarian cancer) resided there. Of the 2,351 eligible women identified, 1,849 were interviewed (78.6%). The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating.

Data collection

In-person interviews pertained to the period of time before diagnosis (for cases) or before an assigned comparable reference date (for controls), and covered the following: demographic and lifestyle characteristics; employment history; medical history; and detailed reproductive history, including menstrual, pregnancy, and use of contraceptive and menopausal hormone preparations.

In addition to start and end dates and average hours per week for each job held at least a continuous four months starting at age 25 until the reference date, participants were asked to report how many of their work days over the duration of the job included the hours between midnight and 4 a.m. (nightshift), to which they could respond: never worked those hours; less than half the days; at least half the days; or every work day. As a measure of chronotype (preference for being active in the morning or the evening), which may be associated with the ability to adapt to nightshift work, participants were asked to report if they were morning persons, evening persons or other (assessed as of 5 years before the reference date).

Shift work variables

For the primary analysis, two shift work variables were created: ever/never worked any nightshift and cumulative nightshift work-years (from age 25 until the reference date). For each participant with j jobs, cumulative nightshift work-years (C_N) was calculated as follows:

$$C_N = [(D_1 \times 4.3\, wks/mos \times H_1 \times F_1)/2080\, hrs\, wrk/yr]_1 + \ldots [(D_j \times 4.3\, wks/mos \times H_j \times F_j)/2080\, hrs\, wrk/yr]_j$$

Where D_j is the total number of months engaged in a particular job, H_j is the hours worked per week for that job and F_j is the fraction of time spent doing nightshift work for that job.

For each job, F_j was assigned as 0 if the subject reported that she never worked nightshifts, 0.25 if she reported that less than half of the days involved nightshifts, 0.5 if she reported that at least half of the days involved nightshifts or 1.0 if she reported that every work day involved nightshifts. Work years were calculated by dividing the total number of hours engaged in nightshift work for a particular job by 2080, which is the total number of hours worked in a year assuming an average of 40 hours of work per week.

We also examined ever/never worked in a job with less than half of work days doing the nightshift and ever/never worked a job with all nightshifts. These categorizations were not mutually exclusive, i.e. a participant reporting working one or more jobs with less than half of works days doing the nightshift and one or more jobs with all nightshifts would be in the "ever" exposed category in both analyses.

Statistical analysis

Unconditional logistic regression was used to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CI). All analyses were adjusted for the frequency-matching variables of age at reference (5-year intervals), county of residence (dichotomized as the three urban or 10 rural/suburban counties in the study) and calendar year of diagnosis/reference date (continuous). We also adjusted for factors known to be associated with ovarian cancer: duration of hormonal contraceptive use (never, <6, 6–59, 60–119 or ≥ 120 months), number of full term pregnancies (0, 1, 2 or ≥ 3) and body mass index (BMI) at age 30 (<18.5, 18.5–24.9, 25–29.9 or ≥ 30). Adjustment for additional factors, including race/ethnicity, history of hormone replacement therapy, smoking status, alcohol use and education had a minimal impact (i.e. < 10% change) on point estimates of interest, so these variables were not included in the final analyses. Cumulative nightshift work-years were categorized according to approximate quartiles among controls who were ever engaged in nightshift work. Median number of work-years was also compared between cases and controls using the Wilcoxon rank-sum test given the highly skewed distribution of the variable.

Additional separate analyses were conducted to examine the association of shift work with risk of ovarian cancer among women diagnosed before and after age 50 years and to examine the association of shift work with tumor subtypes (as described above). We also evaluated whether chronotype (morning or evening preference) modified the association between shift work and ovarian cancer. Participants who did not indicate a morning or evening preference were excluded from this analysis. Effect modification was formally evaluated using likelihood ratio tests comparing models with and without chronotype and nightshift work cross-products terms. All analyses were carried out using the STATA version 11 statistical package (Statacorp LP, College Station, Texas).

Results

After excluding 29 subjects with missing covariate data on BMI, number of births or duration of hormonal contraception, a total of 1,101 invasive cancer cases, 389 borderline tumor cases and 1,832 controls were included in our analyses. The distribution of various characteristics of cases and controls is provided in Table 1. Compared to controls, a lesser proportion of invasive cases used hormonal contraceptives, and invasive and borderline cases tended to have had fewer children than controls. As expected, women with borderline tumors tended to be younger than women with invasive disease.

Among the 27% of invasive cases that reported ever working a night job (Table 2), the median number of work-years engaged in the nightshift was 3.5, and among the 32% of borderline cases, the median number of work-years engaged in the nightshift was 3.2.

Among the 23% of controls working night jobs, the median number of work-years engaged in the nightshift was 2.7; these differences between the case groups and controls were not statistically significant (p >0.5). Among controls and invasive tumor cases, the majority of jobs that were reported as involving nightshift work were in health care (27% and 28%, respectively), mostly nursing, followed by food preparation and service (e.g. cooks, waitresses, bartenders) (18% and 16%) and office and administrative support (e.g. telephone operators, customer service representatives, dispatchers etc.) (17% and 15%). Among borderline cases, the majority of nightshift jobs were in food preparation and service (24%), followed by health care (20%) and office and administrative support (13%).

Ever working the nightshift was associated with a 1.24-fold increased risk of invasive epithelial ovarian cancer (95% CI: 1.04–1.49) and a 1.48-fold increased risk of borderline epithelial ovarian tumors (95% CI: 1.15–1.90). When examining cumulative nightshift work-years, there were no indications of a trend with either invasive or borderline tumors; significant increases in risk were restricted to the second highest cumulative category (>3–7 work-years).

In additional analyses, risks of invasive and borderline tumors among women who reported ever working a job with less than half of the work days as nights ($OR_{invasive}$=1.28, 95% CI: 1.03–1.59; $OR_{borderline}$=1.32, 95% CI: 0.98–1.78) and who reported working a job with all nights ($OR_{invasive}$=1.16, 95% CI: 0.87–1.55; $OR_{borderline}$=1.29, 95% CI: 0.87–1.92) were not materially different from those observed in the main analyses evaluating any history of ever working the nightshift (Table 2). A greater percentage of evening type individuals had ever engaged in nightshift work than had morning types (27% versus 20% of controls; χ^2, p=0.002); while the risks of invasive and borderline ovarian tumors for those ever working the nightshift among self-classified morning type individuals ($OR_{invasive}$=1.29, 95% CI: 1.00–1.67; $OR_{borderline}$=1.57, 95% CI: 1.08–2.27) was slightly greater than those ever working the nightshift among self-classified evening type individuals ($OR_{invasive}$=1.14, 95% CI: 0.85–1.53; $OR_{borderline}$=1.43, 95% CI: 0.97–2.09), the differential effects were not statistically significant ($p_{invasive}$=0.47; $p_{borderline}$=0.54).

When stratifying by reference age, ever working the nightshift was significantly associated with increased risks of both invasive and borderline tumors among women who were 50 years of age or older (Table 3), but risks were not significantly elevated in women under 50 years of age. These apparent differential affects by age were not statistically significant ($p_{invasive}$=0.32; $p_{borderline}$=0.65). Table 4 presents the results of the subtype-specific analyses of invasive and borderline disease. Increased risks of HGSC and LGSC (the latter including borderline and invasive disease) were associated with ever working the nightshift (ORs=1.29, 95% CI: 1.06–1.57, and 1.51, 95% CI: 1.12–2.05, respectively). Risk of MC (including invasive and borderline disease) was also positively associated with ever working the nightshift (OR=1.55, 95% CI: 1.10–2.17). In contrast, overall risks of both EC and CCC were, if anything, slightly reduced in association with ever working the nightshift (OR=0.91 for each of these subtypes). To assess whether subtype-specific differences were simply reflecting an age effect or vice versa, we conducted age-specific analyses within histologic subgroups. No clear differences in risk by age within the EC, CCC, MC and LGSC subgroups were observed, while risks among the most common subtype, HGSC, were primarily increased among women aged 50 or more years (data not shown).

Discussion

In our large population-based case-control study, we found evidence suggesting an association between ever working the nightshift and increased risk of epithelial ovarian tumors. The increased risks that we observed are consistent in magnitude with those

observed for breast cancer in previous studies [18]. However, we did not observe a trend with increasing cumulative duration of nightshift work, nor did we observe an increased risk in the highest category of cumulative duration. There was suggestive evidence that increased risks were restricted to women 50 years of age and older. In tumor subtype analyses, elevated risks associated with nightshift work were observed for HGSC, LGSC and MC subtypes (the latter two including both invasive and borderline tumors), but not with EC or CCC. While risks associated with most reproductive factors have been consistent across all histologic types [19], associations with certain factors such as smoking, endometriosis and BMI have been observed to vary by histology [19–21].

Chronotype has been considered by others as a measure of adaptability to shift work schedules, with evening type individuals reporting better tolerance to nightshift work (e.g. better work performance and higher job satisfaction) than morning type individuals [22]. In the current study, a greater proportion of evening type individuals among our controls had a history of nightshift work, but there was only suggestive evidence that ovarian cancer was elevated to a lesser extent among such individuals than among morning type persons.

In a recent prospective analysis of 718 ovarian cancer cases among 181,548 participants in the Nurse's Health Study, there was no evidence of an association between rotating shift work and ovarian cancer risk [23]. Rotating shift work was defined as working at least 3 nights per month in addition to day or evening shifts and has been previously associated with breast, endometrial and colorectal cancers in the cohort [24–26]. The study did not collect data on permanent/fixed nightshift work. Though our study did not specifically ascertain data on rotating shift work, it is reasonable to assume a rotating shift work schedule for those reporting working jobs with less than half of the work days involving the nightshift. We found evidence of increased risks of invasive ovarian cancer in association with nightshift work even when restricting analyses to this group. It is difficult to directly compare the results of our study to those of the Nurse's Health Study given the differences in shift work data that were collected.

Animal and laboratory data suggest that an increased risk of ovarian cancer associated with circadian disruption may be plausible. In turkey breeder hens with ovarian adenocarcinomas, longer day periods (i.e. longer exposure to light) promoted growth of ovarian tumors, while shorter day periods were found to inhibit growth [27]. Direct administration of melatonin was also found to inhibit tumor growth. As has been hypothesized for breast cancer, melatonin may impact ovarian cancer risk through an effect on endogenous levels of reproductive hormones, particularly estrogen. Though evidence suggests that estrogens may be especially important in the etiology of EC and CCC [6], we did not observe associations between nightshift work and risk of these subtypes. Beyond its effects on reproductive hormones, melatonin has been shown to have direct oncostatic properties. In addition to directly scavenging reactive oxygen and nitrogen species, melatonin stimulates other antioxidants and enzymes that metabolize reactive species [7]. In a study of female rats, ethanol was found to increase lipid hydroperoxide levels in ovarian tissue; with concurrent melatonin administration, lipid hydroperoxide levels were significantly decreased, and the antioxidant activities of superoxide dismutase, glutathione peroxidase and glutathione reductase were all increased [28].

The large size of our study and comprehensive data on historic nightshift schedules, as well as important potential confounders, are strengths. Though participation rates were relatively high for both cases and controls, participation bias may have influenced study results if those women that chose not to participate in our study differed from study subjects in factors related to nightshift work. Although data on nightshift work was retrospectively collected through self-report, the potential association of shift work with ovarian cancer was not a

primary hypothesis of the study that was expressed to participants, so recall bias is unlikely. Further, while study participants may have been aware of light-at-night as a hypothesized risk factor for other cancers, little or no attention had been paid to ovarian cancer during the years in which our study was conducted. The prevalence of shift work in our study population is higher than what has been reported for the general US working population by the Bureau of Labor Statistics (BLS) (17.7% among US salaried workers) [29]. However, the higher prevalence is consistent with the types of jobs that study subjects reported working. For example, among controls, the most commonly worked jobs involving the nightshift were in the health care industry, and according to the BLS, over 24% of salaried health care workers in the US were engaged in shift work in 2004. Food preparation and service was the next most common class of job involving nightshift work that controls reported. According to BLS data, over 49% of salaried US food preparation and service workers were engaged in shift work in 2004.

We did not observe a significant dose-response relationship with cumulative nightshift work-years, which may be attributable to exposure misclassification. For instance, the fraction of time spent working the nightshift for a particular job could, in actuality, be any value between 0 and 1, but for this study, we were only able to assign one of four values to this fraction. Also, information on intensity of nightshift schedules was not ascertained as part of this study, meaning that a participant working a full-time job with 2 nights per week over a period of 10 years would be treated the same in our analyses as a participant working the nightshift for the first 2 years of a full-time job that lasted for 10 years. In addition, the exposure variables, while relatively detailed, may not have captured the aspect of exposure most linked with risk. For example, with rotating shift work schedules, the rate of rotation and direction of rotation may be particularly important [30], but that information was not collected as part of this study. We did, however, have data on chronotype, which may be a critical modifier of the association between nightshift work and cancer but mostly has not been evaluated in studies nightshift work and cancer risk. However, this variable was based on a response to a single question, and there are much more comprehensive assessment tools available such as the Circadian Type Inventory (18-item questionnaire), which assign scores to classify individuals on a morningness-eveningness scale [31]. Chance must also be considered as an explanation of our findings.

We found suggestive evidence that nightshift work is associated with increased risks of both invasive and borderline ovarian tumors, particularly of serous and mucinous subtypes and among women who are 50 years of age and older. However, our results contrast with those of the single prior study of ovarian cancer risk that evaluated rotating shift work. Further research is needed, and future studies should incorporate assessments of chronotype to further explore whether evening-type persons are at a decreased risk of developing ovarian cancer as a result of better adaptability to shift work schedules. These studies should also evaluate the impact of genetic variation in circadian genes in conjunction with chronotype on susceptibility to the potential carcinogenic effects of nightshift work. Prospectively designed studies are likely to provide the best option for collecting the detailed high-quality shift work data that are needed. However, for rare diseases such as ovarian cancer, individual cohorts may lack power to detect significant associations, particularly with respects to stratification on chronotype, genetic variation or tumor morphology.

Acknowledgments

Funding

The study was funded by grants R01 CA112523 and R01 CA87538 from the US National Cancer Institute.

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What this paper adds

- Despite experimental evidence for the effect of circadian disruption on ovarian function, only one previous null study has examined the potential association between shift work and ovarian cancer.
- We found suggestive evidence of an association between a history of nightshift work and both borderline and invasive epithelial ovarian tumors.
- Increased risks were restricted to women who were 50 years of age and older and to serous and mucinous tumor histologies.
- Detailed evaluations of chronotype should be conducted in future studies as it may identify subgroups that are particularly sensitive to the carcinogenic effects of shift work.

Table 1

Demographic factors by case-control status

	Controls (%)(n=1832)		Invasive Cases (%)(n=1101)		Borderline Cases (%)(n=389)	
Age at reference						
35–39	64	(3.5)	38	(3.5)	35	(9.0)
40–44	137	(7.5)	77	(7.0)	53	(13.6)
45–49	243	(13.3)	159	(14.4)	84	(21.6)
50–54	306	(16.7)	187	(17.0)	73	(18.8)
55–59	345	(18.8)	204	(18.5)	60	(15.4)
60–64	330	(18)	221	(20.1)	44	(11.3)
65–69	260	(14.2)	156	(14.2)	30	(7.7)
70–74	147	(8.0)	59	(5.4)	10	(2.6)
Race/ethnicity						
Non-Hispanic White	1663	(90.8)	977	(88.7)	347	(89.2)
Non-Hispanic Black	26	(1.4)	9	(0.8)	5	(1.3)
Non-Hispanic Asian	46	(2.5)	53	(4.8)	11	(2.8)
Non-Hispanic Other	48	(2.6)	28	(2.5)	12	(3.1)
Hispanic	49	(2.7)	44	(3.1)	14	(3.6)
Duration of hormonal contraceptive use						
Never used	310	(16.9)	285	(25.9)	64	(16.5)
<6 months	122	(6.7)	108	(9.8)	29	(7.5)
6 months to <5 years	676	(36.9)	389	(35.3)	143	(36.8)
5 to <10 years	381	(20.8)	192	(17.4)	79	(20.3)
10+ years	343	(18.7)	127	(11.5)	74	(19.0)
No. of full term pregnancies						
0	280	(15.3)	268	(24.3)	102	(26.2)
1	249	(13.6)	188	(17.1)	65	(16.7)
2	617	(33.7)	316	(28.7)	120	(30.9)
3+	686	(37.4)	329	(29.9)	102	(26.2)
BMI at age 30						
<18.5	122	(6.7)	64	(5.8)	23	(5.9)
18.5–24.9	1393	(76.0)	807	(73.3)	265	(68.1)

	Controls (%)(n=1832)		Invasive Cases (%)(n=1101)		Borderline Cases (%)(n=389)	
25–59.9	211	(11.5)	133	(12.1)	66	(17.0)
30+	106	(5.8)	97	(8.8)	35	(9.0)
Highest attained education						
High school or less	395	(21.6)	266	(24.2)	102	(26.2)
Some college	672	(36.7)	393	(35.7)	152	(39.1)
College graduate	442	(24.1)	260	(23.6)	92	(23.7)
Post graduate	321	(17.5)	179	(16.3)	43	(11.1)
Unknown	2	(<1)	3	(<1)	0	(0)
Total number of jobs worked over lifetime						
0	62	(3.4)	40	(3.6)	12	(3.1)
1	307	(16.8)	186	(16.9)	76	(19.5)
2	405	(22.1)	207	(18.8)	87	(22.4)
3	351	(19.2)	224	(20.4)	74	(19.0)
4	269	(14.7)	159	(14.4)	54	(13.9)
≥5	438	(23.9)	285	(25.9)	86	(22.1)
Chronotype						
Morning type	972	(53.1)	584	(53.0)	183	(47.0)
Evening type	652	(35.6)	411	(37.3)	179	(46.0)
Other	207	(11.4)	106	(9.6)	27	(6.9)
Don’t know	1	(<1)	0	(0)	0	(0)

Table 2

Risk of invasive and borderline ovarian tumors in association with working the nightshift

	Invasive					Borderline		
	Controls (%)(n=1832)		Cases (%)(n=1101)		OR[a] (95% CI)	Cases (%)(n=389)		OR[a] (95% CI)
Worked nightshift								
Never	1420	(77.5)	808	(73.4)		263	(67.6)	
Ever	412	(22.5)	293	(26.6)	1.24 (1.04–1.49)	126	(32.4)	1.48 (1.15–1.90)
Worked nightshift for less than half of all work days								
Never	1587	(86.6)	916	(83.2)		312	(80.2)	
Ever	245	(13.4)	185	(16.8)	1.28 (1.03–1.59)	77	(19.8)	1.32 (0.98–1.78)
Worked nightshift for all work days								
Never	1696	(92.6)	1006	(91.4)		351	(90.2)	
Ever	136	(7.4)	95	(8.6)	1.16 (0.87–1.55)	38	(9.8)	1.29 (0.87–1.92)
Cumulative nightshift work-years								
Never	1420	(77.5)	808	(73.4)		263	(67.6)	
4mos-1 yr	97	(5.3)	55	(5.0)	1.03 (0.72–1.47)	27	(6.9)	1.44 (0.90–2.29)
>1–3 yrs	121	(6.6)	75	(6.8)	1.13 (0.82–1.54)	35	(9.0)	1.33 (0.87–2.02)
>3–7 yrs	85	(4.6)	94	(8.5)	1.95 (1.41–2.68)	44	(11.3)	2.37 (1.57–3.57)
>7 yrs	108	(5.9)	68	(6.2)	1.02 (0.74–1.42)	20	(5.1)	0.97 (0.58–1.61)
unknown	1	(<1)	1	(<1)	-	0	(0)	-

[a]Adjusted for age at reference, county, reference year, duration of oral contraceptive use, number of full term pregnancies and BMI at age 30

Table 3

Risk of invasive and borderline ovarian tumors, by age at reference date, in association with working the nightshift

	<50 years of age at reference date						≥50 years of age at reference date					
	Invasive			Borderline			Invasive			Borderline		
	Controls (%)(n=444)	Cases (%)(n=274)	OR[a] (95% CI)	Cases (%)(n=172)	OR[a] (95% CI)		Controls (%)(n=1388)	Cases (%)(n=827)	OR[a] (95% CI)	Cases (%)(n=217)	OR[a] (95% CI)	
Worked nightshift												
Never	326 (73.4)	197 (71.9)		113 (65.7)			1094 (78.8)	611 (78.8)		150 (69.1)		
Ever	118 (26.6)	77 (28.1)	1.0 (0.69–1.44)	118 (26.6)	1.38 (0.92–2.05)		294 (21.2)	216 (21.2)	1.32 (1.07–1.63)	67 (30.1)	1.57 (1.13–2.19)	
Cumulative nightshift work-years												
Never	326 (73.4)	197 (71.9)		113 (65.7)			1094 (78.8)	611 (73.9)		150 (69.1)		
4mos-1 yr	26 (5.9)	16 (5.8)	1,06 (0.52–2.15)	12 (7.0)	1.28 (0.61–2.71)		71 (5.1)	39 (4.7)	0.98 (0.65–1.49)	15 (6.9)	1.51 (0.83–2.76)	
>1–3 yrs	44 (9.9)	22 (8.0)	0.82 (0.45–1.49)	20 (11.6)	1.28 (0.70–2.34)		77 (5.6)	53 (6.4)	1.26 (0.89–1.84)	15 (6.9)	1.32 (0.73–2.40)	
>3–7 yrs	24 (5.4)	28 (10.2)	1.52 (0.81–2.87)	22 (12.8)	2.36 (1.22–4.57)		61 (4.4)	66 (8.0)	2.04 (1.40–2.97)	22 (10.1)	2.34 (1.36–4.01)	
>7 yrs	24 (5.4)	11 (4.0)	0.67 (0.30–1.51)	5 (2,9)	0.63 (0.22–1.74)		84 (6.1)	57 (7.0)	1.16 (0.80–1.66)	15 (6.9)	1.29 (0.71–2.33)	
unknown	0 (0)	(0) (0)	-	0 (0)	-		1 (<1)	1 (<1)	-	0 (0)	-	

Reference date is the date of diagnosis among cases and a comparable assigned date among controls

[a]Adjusted for age at reference, county, reference year, duration of oral contraceptive use, number of full term pregnancies, and BMI at age 30

Table 4

Risk of invasive and borderline ovarian cancer, by tumor subtype, in association with working the nightshift

			High Grade Serous			Low Grade and Borderline Serous[b]			Invasive and Borderline Mucinous[c]			Endometrioid			Clear Cell		
	Controls (%)(n=1832)		Cases (%)(n=834)		OR[a] (95% CI)	Cases (%)(n=240)		OR[a] (95% CI)	Cases (%)(n=181)		OR[a] (95% CI)	Cases (%)(n=129)		OR[a] (95% CI)	Cases (%)(n=83)		OR[a] (95% CI)
Worked nightshift																	
Never	1420	(77.5)	606	(72.7)		161	(67.1)		121	(66.8)		100	(77.5)		64	(77.1)	
Ever	412	(22.5)	228	(27.3)	1.29 (1.06–1.57)	79	(32.9)	1.51 (1.12–2.05)	60	(33.1)	1.55 (1.10–2.17)	29	(22.5)	0.91 (0.57–1.43)	19	(22.9)	0.91 (0.52–1.59)
Cumulative nightshift work-years																	
Never	1420	(77.5)	606	(72.7)		161	(67.1)		121	(66.9)		100	(77.5)		64	(77.1)	
4mos-1 yr	97	(5.3)	39	(4.7)	0.97 (0.65–1.44)	16	(6.7)	1.34 (0.76–2.38)	11	(6.1)	1.29 (0.66–2.51)	8	(9.2)	1.31 (0.59–2.90)	6	(7.2)	1.38 (0.55–3.43)
>1–3 yrs	121	(6.6)	50	(6.0)	1.01 (0.71–1.44)	23	(9.6)	1.41 (0.86–2.31)	18	(9.9)	1.46 (0.85–2.53)	12	(5.8)	1.34 (0.68–2.65)	7	(6.0)	1.06 (0.44–2.54)
>3–7 yrs	85	(4.6)	83	(10.0)	2.30 (1.65–3.21)	25	(10.4)	2.24 (1.36–3.71)	20	(11.1)	2.46 (1.43–4.2)	5	(3.9)	0.61 (0.23–1.66)	3	(3.6)	0.60 (0.17–2.11)
>7 yrs	108	(5.9)	55	(6.6)	1.09 (0.77–1.55)	15	(6.3)	1.18 (0.66–2.13)	11	(6.1)	1.12 (0.58–2.18)	4	(3.1)	0.43 (0.15–1.24)	3	(3.6)	0.59 (0.17–1.98)
unknown	1	(<1)	1	(<1)	-	0	(0)	-	0	(0)	-	0	(0)	-	0	(0)	-

*23 cases with unspecified borderline tumors excluded

[a]Adjusted for age at reference, county, reference year, duration of oral contraceptive use, number of full term pregnancies, and BMI at age 30

[b]Low Grade Serous n = 23, Borderline Serous n = 217

[c]Invasive Mucinous n = 32, Borderline Mucinous n = 149