Published in final edited form as:

Psychosom Med. 2017 ; 79(9): 1059–1067. doi:10.1097/PSY.0000000000000464.

The association of work characteristics with ovarian cancer risk and mortality

Claudia Trudel-Fitzgerald, PhD¹, Elizabeth M. Poole, PhD², Annika Idahl, MD, PhD³, Eva Lundin, MD⁴, Anil K. Sood, MD⁵, Ichiro Kawachi, MB.ChB, PhD¹, Laura D. Kubzansky, PhD, MPH¹, and Shelley S. Tworoger, PhD^{2,6}

¹Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States

²Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States

³Department of Clinical Sciences, Obstetrics and Gynecology, Umeå University, Umeå, Sweden

⁴Department of Medical Biosciences, Pathology, Umeå University, Umeå, Sweden

⁵Department of Gynecologic Oncology and Reproductive Medicine, Division of Surgery, The University of Texas MD Anderson Cancer Center, Houston, Texas, United States

⁶Department of Epidemiology, Harvard T.H. Chan School of Public Health Boston, Massachusetts, United States

Abstract

Objective—Ovarian cancer (OvCA) is a leading cause of cancer death for women. Depression and social isolation have been associated with a higher OvCA risk and poorer survival, but other forms of chronic psychosocial stress, including work-related characteristics, remain understudied.

Methods—Women from three prospective cohorts (Nurses' Health Study (NHS), n=31,754; Nurses' Health Study II (NHSII), n=74,260; Northern Sweden Health and Disease Study (NSHDS); nested case-control study=196) completed a job questionnaire, assessing demand and control at work, social support provided by coworkers and supervisor, and job security. Multivariate Cox and conditional logistic regression models estimated hazard ratios (HR; NHS/NHSII) and odd ratios (OR; NSHDS) of OvCA risk and mortality among cases. Random coefficient models were used for meta-analyses.

Results—There were 396 OvCA cases and 186 deaths during follow-up. Overall, job strain, strain chronicity, social support and job security were not significantly associated with OvCA risk (e.g., pooled $RR_{\text{high demand/low control}}=1.06$; $CI=0.72,1.55$) or mortality (e.g., pooled $RR_{\text{high demand/low control}}=1.08$; $CI=0.64,1.82$). When considered individually, compared to low levels, only moderate levels of demand were associated with a reduced OvCA relative risk (pooled $RR=0.66$; $CI=0.49,0.90$). Social support provided by the coworker or the supervisor did not moderate the association of job strain with either OvCA risk or overall mortality.

Conflicts of interest: Authors do not have any potential conflicts of interest to report.

Conclusion—We did not observe clear associations between work characteristics and OvCA incidence or mortality, but further research with diverse populations is warranted.

Keywords

control; demand; job strain; mortality; ovarian cancer; social support

Ovarian cancer (OvCA) is the fifth leading cause of cancer death in the United States (1–3). Every year, there are around 11.9 new OvCA cases and 7.5 deaths per 100,000 American women (1–3). The rates are similar for many European countries (e.g., 10.3 new cases and 8.2 deaths per 100,000 women ascertained in Sweden in 2012) (4). A limited number of risk factors have been identified, including family history of breast and ovarian cancer, nulliparity, smoking, and obesity, in addition to protective factors like oral contraceptive use and tubal ligation (1,3). However, strategies for detection of early-stage disease and treatment of advanced stages remain limited (1,5) and many known determinants are not alterable. Hence, identifying additional modifiable risk factors that may potentially affect OvCA development/progression is critically needed to reduce incidence and mortality.

Studies in experimental animal model and in OvCA patients have suggested that biologic changes associated with chronic psychosocial stress and distress may influence carcinogenesis. For example, mice under chronic stress (via physical restraint or social isolation) had larger and more aggressive ovarian tumors compared to control animals, which appeared to act through the β_2 -adrenergic receptor (6–8). This effect seems to be largely due to stress-related sympathetic nervous system activation of norepinephrine, which can directly influence tumor progression by affecting cellular adhesion, cell migration, invasion, and angiogenesis (9,10). Moreover, activation of stress signaling may influence OvCA via other mechanisms, like reducing natural killer cell activity (10,11) or suppressing wound healing (12). Further, OvCA patients who were distressed or socially isolated had immune function dysregulation and worse survival (13–16), and a recent Nurses' Health Studies (NHS/NHSII) report showed an increased OvCA risk among those with versus without depression (17).

Nevertheless, little prospective research has considered the potential impact of chronic stressors on OvCA risk, including those that can emanate from the work environment. Given the changes in the workplace that occurred with industrialization, psychosocial work experiences have become increasingly studied as health determinants (18). Both brief and lasting unfavorable working conditions, including elevated job demands, limited control, job insecurity and poor social support from colleagues and supervisors, have been significantly related to sustained mental health problems (19,20), reflecting the potential chronic nature of work-related stress. Prior research on these stressors and physical health outcomes has most commonly tested these effects following Karasek and Theorell's theory of job strain. These studies usually characterize job strain according to levels of exposure to job-related demands and control (18,21,22) to test whether work-related stress, as defined by high strain, might increase risk of developing chronic diseases. Several meta-analyses of studies with large sample sizes and covering long follow-up periods showed consistent evidence that individuals who report high strain jobs (those that impose high demands but permit little

control over workflow or other aspects of the job) as well as job insecurity, have greater cardiovascular risk (23–25). Additionally, studies have considered another job-related psychosocial factor, low social support at work, either as an independent determinant or in combination with job strain, and has found it is associated with increased risk of heart disease (18,26).

Numerous studies have also considered job strain in relation to cancer-related outcomes. A meta-analysis of 12 European cohort studies observed that among studies that assessed job strain a one time point, high strain was not associated with colorectal, lung, breast, or prostate cancer (27). This is consistent with results from the NHS that reported no association of job strain with breast cancer incidence (28,29), although a Swedish cohort observed a 40% increased breast cancer risk in women with higher versus lower stress jobs (30). These mixed findings on the relationship between work stress and incident breast cancer point to the possibility that cultural (American vs. Swedish) or occupational (nurses only vs. heterogeneous jobs) differences between these populations may lead to different effects of job strain, suggesting the importance of additional research using a varied cultural/occupational sample. Moreover, studies have reported that work-related stress, as measured for example by high demand and insecurity, is associated with greater odds of bladder and stomach cancer (31), and higher risk of certain subtypes of esophageal cancers (32). While these studies have some limitations (e.g., use of retrospective stress assessment), they do suggest that workplace stressors may relate to certain cancers.

Despite suggestive findings from animal models and some human studies on potential toxic effects of chronic stress (e.g., distress, social isolation) in relation to OvCA, job strain has not been examined specifically in relation to OvCA risk or survival among cases. Therefore, we conducted a prospective study of work characteristics with risk of and survival after OvCA in the NHS/NHSII (work aspects assessed twice) and in a Swedish cohort, the Northern Sweden Health and Disease Study (NSHDS). To acknowledge the role of known contributors of OvCA risk and of potential confounders in the relation of work characteristics with physical health outcomes, we followed prior work (11,17,25) and considered various covariates in our statistical analyses.

METHODS

Participants

U.S. Samples—The ongoing NHS cohort comprised of 121,700 female nurses, enrolled in 1976 (ages 30–55 years) (33). Similarly, the NHSII began in 1989 among 116,430 younger female registered nurses (ages 25–44 years) (34). All women complete biannual questionnaires on demographic characteristics, lifestyle, medical history and newly diagnosed medical conditions, with an overall response rate of >85% (35). The present study includes initially cancer-free (except non-melanoma skin cancer) women with at least one ovary who responded to at least one job strain questionnaire (NHS: $N=31,754$; NHSII: $N=74,260$). The study protocol was approved by the institutional review board of the Brigham and Women's Hospital.

Swedish Sample—A nested case-control study was conducted within the prospective Northern Sweden Health and Disease Study (NSHDS), which is comprised of 3 population-based sub-cohorts, the Västerbotten Intervention Programme cohort, Monitoring Trends and Determinants in Cardiovascular Disease cohort, and the mammary screening cohort (36). These sub-cohorts cover a range of occupational statuses. For instance, the broad socioeconomic distribution in the Västerbotten Intervention Programme cohort includes categories analogous to part-time jobs and manual work (i.e., unskilled laborers, ~30%; skilled laborers, ~17%; lower employees, ~13%), to clerical, service and blue collars jobs (i.e., in-between employees, ~18%), to professional, administrative, support and sales jobs (i.e., higher employees, ~11%), and a category of unknown occupations (~12%) (37). Its distribution of education levels is also diverse (i.e., Did not complete upper secondary [high] school, ~33%; Completed upper secondary [high] school, ~40%; More than upper secondary [high] school, ~23%) (37). No significant differences in socioeconomic groups and education levels were reported compared to non-participants (37).

All NSHDS participants provided information on demographic characteristics, lifestyle and medical history at baseline enrollment. Cases were identified through the Swedish Cancer Register and selected if they had prospectively participated in the NSHDS. Controls, without a cancer diagnosis (except basalioma) and with at least one ovary at the time the case was diagnosed, were matched on year of birth and date of completing the questionnaire (38). Both OvCA cases and matched controls then retrospectively provided information on key OvCA risk factors, including contraceptive use and familial history of cancer. We included OvCA cases (n=102) and controls (n=94) who completed the job strain questionnaire at baseline. The study was approved by the Human Ethics Committee of the Medical Faculty, Umea University, Sweden.

Measures

Work Characteristics—Karasek and Theorell's job content questionnaire (JCQ) (22), queried twice in NHS (1992/1996) and NHSII (1993/1997), assesses psychological workload (demand) of a job and level of control available for managing the workload. The demand dimension is derived by summing 5 items evaluating excessive work, conflicting demand, insufficient time to work, fast pace, and working hard. The control dimension is derived based on 9 items evaluating skill discretion (e.g., learning new things, potential to develop new skills, work not being repetitious) and decision authority (e.g., freedom to make decisions, choice about how to perform work). Except for 1997 (NHSII), participants also indicated the extent to which they received work-related social support from coworkers and supervisors. All answers ranged from (1) "strongly disagree" to (4) "strongly agree". Psychometric properties of the JCQ have been reported elsewhere (22,39). In our samples, internal consistency reliability coefficients at baseline are strong (NHS: $\alpha_{demand}=0.74$; $\alpha_{control}=0.81$; $\alpha_{coworkers}=0.82$; $\alpha_{supervisor}=0.91$; NHSII: $\alpha_{demand}=0.73$; $\alpha_{control}=0.80$; $\alpha_{coworkers}=0.82$; $\alpha_{supervisor}=0.91$).

We followed Karasek & Theorell's job demand and control model to characterize job strain exposure. Accordingly, demand and control levels were categorized as above or below the median of responses, creating a 2×2 exposure matrix: "high strain" (high demand, low

control; the most stressful), “active” (high demand, high control), “passive” (low demand, low control) and “low strain” (low demand, high control; the least stressful). We also considered the demand and control subscales separately, in tertiles (21,40). Additionally, a single item queried to what extent nurses perceived their job security as good (NHS: 1992/1996/2000; NHSII: 1993/1997/2001).

The Theorell Questionnaire (DCQ) (41), a Swedish modification of the JCQ, was completed by NSHDS participants at recruitment. This included 4 items representing the demand dimension (e.g., conflicting demand, insufficient time to work) and 6 items reflecting the control dimension (e.g., learning new things, having a job requiring skill, work not being repetitious, freedom to make decisions). While derived from a similar theoretical framework, this scale had minor discrepancies in wording and numbers of questions than the JCQ (42). Hence, following prior work we generated comparable scale scores between the JCQ and DCQ by (42): 1) matching response distributions of DCQ questions with equivalent JCQ questions; 2) using a weighting strategy to compensate for differing number of questions; 3) transforming DCQ scores on a Z-distribution to eliminate remaining important differences. Internal consistency reliability coefficients were modest ($\alpha_{demand}=0.70$; $\alpha_{control}=0.39$) in NSHDS.

Covariates—Available NHS/NHSII covariates included age (continuous), census-tract income (a proxy for socioeconomic status; continuous), marital status (single/divorced/separated/widowed vs. married/partnership), oral contraceptive use duration (OC; continuous), parity (continuous), tubal ligation (no/yes), familial history of breast or ovarian cancer (no/yes), menopausal status (premenopausal or unknown/postmenopausal), hormone therapy use duration (HT; continuous), body mass index (BMI; kg/m²; continuous), physical activity (MET-hour/week; continuous), caffeine consumption (g/day; continuous), caloric intake (kcal/day; continuous), alcohol consumption (g/day; continuous), and smoking status (never/former/current). Covariates were self-reported at study baseline (NHS=1992; NHSII=1993) and generally updated at subsequent questionnaire cycles until the end of follow-up. Sensitivity analyses also adjusted for depression symptoms, measured three times in the NHS cohorts (NHS: 1992/1996/2000; NHSII: 1993/1997/2001) using the five-item Mental Health Index (MHI-5) from the Medical Outcomes Study Short-Form 36 Health Status Survey (43).

In NSHDS, selected covariates were: age (continuous), marital status (single/divorced/separated/widowed vs. married/partnership), highest education level (a proxy for socioeconomic status; high school/some college or completed college or post graduate), OC use duration (continuous), parity (continuous), tubal ligation (no/yes), family history of breast or ovarian cancer (no/yes), menopausal status (premenopausal or unknown/postmenopausal), HT use (ever/never), BMI (kg/m²; continuous), physical activity (active/moderately active vs. inactive/moderately inactive), alcohol consumption (g/day; continuous), and smoking status (never/former/current). Reproductive variables were queried of cases and matched controls after case diagnosis; all other covariates were self-reported at baseline.

Ascertainment of Cases and Deaths—Among the NHS/NHSII, incident OvCA cases were defined as having a diagnosis after the return of the first completed questionnaire that assessed work characteristics and before 2012 or 2011, respectively. All women who reported having an OvCA diagnosis on biennial questionnaires were asked permission to review their pathology reports and medical records by a blinded gynecologic pathologist to confirm the diagnosis and assess tumor characteristics (e.g., stage, histology), with high concordance between reviews of pathology records and surgical pathology slides (44). Deaths were reported by next of kin and postal authorities or identified through the National Death Index, leading to 98% mortality follow-up (45). In the NSHDS study, incident cases were selected using the Swedish Cancer Registry (46). Histopathologic diagnoses were reviewed by a specialist in gynecologic pathology at the Department of Medical Biosciences, Pathology, Umeå University, and deaths were identified by the Swedish Cause of Death Registry with >95% follow-up (47). The distribution of histology for cases within the NHS and NSHDS cohorts is somewhat comparable to the distribution in their wider respective populations (e.g., serous cases: NHS=53.7% vs U.S. population=45.9%; NSHDS=34.7% vs. Swedish population=41.7%) (2,48). The mortality rate in the NHS cohorts is similar to U.S. rates broadly (10 vs. 8 deaths per 100,000 person-years); however, NSHDS rates cannot be compared to the general Swedish population given the case-control study research design (2,4).

Statistical analyses

All analyses were conducted using SAS[®] software version 9.4 with a two-sided p-value of 0.05. Descriptive analyses at baseline were assessed across the four job strain categories for each cohort separately.

OvCA Incidence—Cox proportional hazards regression models assessed the hazard ratios (HR) and 95% confidence intervals (CI) of incident OvCA among NHS/NHSII, until end of follow-up (2012/2011), incident OvCA diagnosis, or bilateral oophorectomy, whichever came first. The association of time-updated work characteristics, including job strain categories, as well as demand and control separately, with OvCA risk was examined in four sets of models to evaluate in more detail the role of various covariates. An initial model adjusted for age only; the next adjusted for demographics (age, marital status, income). We then added hormonal-related variables (OC use, parity, tubal ligation, family history of breast or ovarian cancer, menopausal status, HT use) and a final model included behavior-related covariates (BMI, physical activity, smoking status, caffeine, calories, alcohol intake). As both cohorts yielded similar results, data were pooled for the final analyses.

Conditional logistic regression models were used to evaluate the odds ratios (OR) and 95% CI of incident OvCA in the NSHDS case-control study. Four analogous model sets to those used among the NHS cohorts were investigated, although there were slight differences: a) education level rather than income was used; b) HT use and tubal ligation were not included given their low frequency (<5%); and c) caffeine and calories intake were not available in NSHDS. Because findings were robust across age- and demographic-adjusted models in the NHS/NHSII and NSHDS, only the last two models are presented (labeled herein Models 1 and 2).

Overall Mortality—Cox proportional hazards regression models estimated the HR and 95% CI of mortality among OvCA cases, until the end of follow-up period (NHS=2012; NHSII=2011; NSHDS=2014) or death, whichever came first. We used the same exposure variables and covariates, with further adjustment for cancer stage and histology.

Meta-Analyses—Fully-adjusted multivariable estimates and their associated standard error from the NHS/NHSII and NSHDS were pooled using random-effects in meta-analyses, providing relative risks (RR). Specifically, the studies are weighted proportionately to the inverse of the sum of the study specific variance plus the common between-studies variance, to consider the different research design used by NHS/NHSII vs. NSHDS. The Cochrane Q statistic was used to assess the heterogeneity of the associations among the cohorts.

Secondary Analyses—Among the NHS cohorts, further analyses explored potential differences due to histology (serous vs. non-serous tumors). Additionally, the role of job security (yes/no) and strain chronicity (categories based on the two assessments: “Stable low strain” (reference group) vs. “Mixed trajectories” vs. “Stable high strain”) was examined in relation to OvCA risk and overall mortality. Lastly, coworkers and supervisor social support were considered separately as independent determinants (tertiary) or effect modifiers of the relationship between job strain and the outcomes in stratified analyses (high vs. low/moderate support).

RESULTS

Baseline Characteristics

At the 1992 baseline, NHS women were 55.3 years old on average ($SD=6.0$; range 45.5–72.3). The majority were married (80.6%), postmenopausal (60.9%) and had previously used OCs (59.9%). NHSII women were younger at baseline in 1993 (mean age=38.4 years; $SD=4.7$; range 28.5–47.8), most were married (90.9%) and had ever used OCs (85.3%), but only 1.1% were postmenopausal. The NSHDS sample had a mean age of 49.8 years ($SD=8.1$; range 29.9–60.8), included mostly married women (86.7%), with 40.8% being postmenopausal and 48.0% being ever OC users. Table 1 presents the distribution of key OvCA risk factors across job strain categories at baseline.

OvCA risk

Within the NHS cohorts, 294 OvCA cases were documented over the 20-year follow-up period (median 4.5 years between latest job strain assessment completed and OvCA diagnosis). Compared to nurses categorized as “Low Strain”, those with “Passive”, but not “High Strain” or “Active”, jobs had a significant 55% higher OvCA risk, after adjusting for sociodemographic, hormonal variables and health behaviors (Table 2, Models 1 and 2). When considering the demand and control subscales independently, control levels were not significantly associated with OvCA risk. However, nurses reporting moderate or high demand jobs had a significant 26% to 36% lower OvCA risk. Similar results were obtained when cohorts were investigated separately (see Table, Supplemental Digital Content 1).

In the NSHDS, there were 102 OvCA cases (median 8.0 years between job strain assessment and OvCA diagnosis). No significant associations were observed for job strain categories (e.g., $OR_{Low\ Strain\ fully-adjusted}=0.36$; $CI=0.04, 3.40$), nor for subscales separately.

In the meta-analysis, only moderate (vs. low) level of demand was significantly associated with OvCA risk ($RR=0.66$; $CI=0.49, 0.90$). No significant associations of job strain categories with OvCA risk were evident. All tests for heterogeneity across studies were non-significant ($P>.05$).

Overall Mortality

There were 138 deaths (94% due to OvCA) over follow-up among NHS/NHSII cases (median 2.9 years between OvCA diagnosis and death). No association was observed between either job strain categories or the demand and control subscales and subsequent mortality (e.g., $HR_{High\ demand\ fully-adjusted}=1.31$; $CI=0.86, 2.00$; see Tables, Supplemental Digital Content 2 [mortality analyses], Supplemental Digital Content 1 [results by cohort]). Similarly, null associations were observed for work characteristics and mortality in NHSDS ($N_{deaths}=48$; 85% due to neoplasms of genital organs; median 2.0 years between OvCA diagnosis and death) and in the meta-analysis. The Q statistic revealed no significant heterogeneity across studies ($P>.05$).

Secondary Analyses

Within the NHS/NHSII, we observed no associations of either job strain categories or demand and control subscales with OvCA risk by subtype ($N_{serous\ cases}=158$; $N_{non-serous\ cases}=136$; see Table, Supplemental Digital Content 3) with one exception. Moderate and high levels of demand were unexpectedly associated with a significant 32% to 39% reduced serous OvCA risk. No clear associations of work characteristics were noted with mortality ($N_{serous\ deaths}=87$, $N_{non-serous\ deaths}=51$; see Table, Supplemental Digital Content 4). Compared to women who reported “Stable low strain”, those who reported “Stable high strain” or “Mixed trajectories” jobs did not have higher multivariate OvCA risk ($HR_{high\ strain}=0.96$, 95% $CI=0.46, 2.02$, $HR_{mixed}=1.53$, 95% $CI=0.81, 2.89$) or overall mortality ($HR_{high\ strain}=2.11$, 95% $CI=0.68, 6.59$, $HR_{mixed}=1.09$, 95% $CI=0.40, 2.94$). Moreover, we observed null associations of insecure job and social support with OvCA risk (e.g., $HR_{insecure\ job}=1.07$; $CI=0.79, 1.45$; $HR_{High\ coworkers\ support\ fully-adjusted}=1.00$; $CI=0.71, 1.41$; see Table, Supplemental Digital Content 5). However, an insecure job ($HR_{fully-adjusted}=0.57$; $CI=0.35, 0.92$), but not social support, was related to reduced risk of mortality among nurses with OvCA. Social support did not moderate the association of job strain categories with either OvCA risk or overall mortality ($p_{interaction}>.05$; results not shown). Finally, considering depression as a potential confounder yielded similar parameter estimates in fully-adjusted models for the relationship of job strain with OvCa incidence and overall mortality (e.g., OvCA risk: $HR_{Passive\ jobs}=1.54$; 95% $CI=1.05, 2.27$), as did excluding women with high depression levels at baseline (e.g., OvCA risk: $HR_{Passive\ jobs}=1.61$; 95% $CI=1.05, 2.47$; see Table, Supplemental Digital Content 6).

DISCUSSION

Because job strain may capture facets of psychosocial stress that affect health as demonstrated by consistent associations with cardiovascular disease risk and mortality among individuals mostly from the U.S. and Europe (23–25), and because OvCA seems susceptible to stress-related biological alterations, we hypothesized stress-related work characteristics would be associated with increased risk of incident OvCa and mortality. In the current meta-analyses based on samples of American and Swedish women, moderate versus low level of demand was significantly related to a 34% reduced OvCA risk. We observed mostly null associations for OvCA outcomes with all other job stress exposures, with the exception of one unexpected finding of lower mortality risk associated with higher job insecurity. However, in the context of our other findings and given the relatively low power of this analysis (only 25 women reported job insecurity), we believe these results are likely due to chance. Our findings are in fact consistent with prior work considering job strain with cancer incidence, which has mostly observed null associations (27–29). This apparent outcome specificity may be due to different stress-activated biologic mechanisms (24).

Accordingly, work-related stress has been linked to lower heart-rate variability and higher haemoglobin A1c, which are key pathways to cardiovascular outcomes, whereas results have been inconsistent for stress response hormones, including cortisol, testosterone, prolactin, and catecholamines (49,50). Up-regulation of catecholamines, specifically norepinephrine and activation of β -adrenergic pathways (7–10), is a primary mechanism of the stress-OvCA linkage. Our findings may suggest that job strain does not activate the specific stress systems that alter OvCA risk. In that case, the null finding reported here may be a true null; this would be consistent with findings that other psychosocial stressors associated with higher catecholamine levels are related to OvCA risk. For example depression, which has been associated with higher catecholamine levels (51,52), was also related to increased OvCA risk in NHS/NHSII (17). Observational data on depression and lower social support also suggested relationships with biomarkers of worse OvCA prognosis or reduced survival (14,16). Another explanation for null associations detected within our populations is that job strain was assessed before OvCA diagnosis but because many women may stop working after diagnosis, job strain effects are no longer in play.

Findings may also reflect methodological artifacts. First, various exposures can be generated from the Job Content Questionnaire items (21,40). The high-strain job category (high demand, low control), conventionally considered as the most stressful level, has generally not been associated with cancer endpoints. However, misclassification might have occurred; national means collected in U.S. female workers were comparable to ours among U.S. nurses for the control subscale, but were considerably higher for demand (demand_{study} = 12, control_{study} = 27 vs. demand_{national} = 31, control_{national} = 30) (40). Hence, because our “high strain” group appears less distressed than do other populations, associations may be harder to detect. Other characteristics including work-life balance (53) and working hours (54) may provide additional insight into relationships between work conditions and OvCA outcomes.

Second, given our use of three occupational samples, null findings may be due to a “healthy worker effect” (55), whereby unhealthy women would not engage in/maintain a profession over time. Given the age at which women were first asked about work-related stress, women remaining in high demand jobs may cope more easily with the workload. However, there were no differences between the older and younger NHS cohorts on job strain-OvCA relationship, suggesting that early versus late stage career does not have a strong impact, at least among nurses. Future research might consider work-related stress earlier in the career and with varied occupations.

Moreover, nurses, who are overrepresented in this study, may be more emotionally resilient compared to other working women (56). This positive capacity to cope with stress was not assessed in NHS/NHSII, but could buffer strain stemming from highly demanding work conditions and, consequently, effects on physical health. Further, nurses have reported appreciating an occupation that fosters autonomy, empowerment and decision-making opportunities (57), potentially explaining the *decreased* OvCA risk noted for moderate-to-high versus low levels of demand within this population. Similarly, an inactive job with a low level of workload and autonomy may cause distress among nurses, possibly explaining the 55% increased OvCA risk among the passive vs. the low-strain category in the NHS/NHSII. Finally, nurses may exhibit greater conscientiousness (e.g., show self-discipline) particularly with regard to health factors than other working women (56), which could increase adherence to a healthy lifestyle and regular medical screenings. Together, these traits might explain why work characteristics were not clearly associated with cancer endpoints in these NHS/NHSII women, and even with CVD outcomes in those cohorts (58). As for the NSHDS null results, if the job strain effects exist and are indeed small, they would be difficult to detect with this smaller sample size.

Strengths of our study included the use of a longitudinal design and multiple cohorts. Updated exposure assessments in NHS/NHSII women with prospective follow-up for 20 years minimized potential reverse causation and recall biases. Moreover, including a European sample permitted assessment across populations and job types. We also considered several potential confounders, including known OvCA determinants and behavioral correlates of stress.

Together, the current findings do not support stress-related work characteristics as an important determinant of OvCA risk or mortality among cases. Given preliminary data supporting the role of distress and social isolation on immune function and biomarkers, which consequently affect tumor progression, further research could consider other ways of characterizing the work environment (e.g., work-life balance) and explore additional psychosocial risk factors with OvCA etiology. Identifying modifiable determinants is still needed to allow more targeted and efficient prevention strategies for this deadly disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding: This work was supported by R01 CA163451 by the National Institute of Health as well as by Department Of Defense W81XWH-13-1-0493. The Nurses' Health Study is supported by grants UM1 CA186107 and P01 CA87969, while the Nurses' Health Study II is supported by grant UM1 CA17672 by the National Institute of Health. The NHSDS study was supported by grants from the Cancer Research Foundation in Northern Sweden. CTF received a postdoctoral fellowship from the Canadian Institutes of Health Research. We would like to thank the participants and the staff of the Nurses' Health Study, Nurses' Health Study II and the Northern Sweden Health and Disease Study for their valuable contributions as well as the following American state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. The authors do not have any potential conflicts of interest to report.

Acronyms

BMI	body mass index
CI	confidence intervals
HR	hazard ratio
HT	hormone therapy
OC	oral contraceptive
OR	odd ratio
OvCA	ovarian cancer
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
NSHDS	Northern Sweden Health and Disease Study
RR	relative risk
SD	standard deviation

References

1. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016.
2. Howlader, N., Noone, A., Krapcho, MDM., Bishop, K., Altekruse, S., Kosary, C., Yu, M., Ruhl, J., Tatalovich, Z., Mariotto, A., Lewis, D., Chen, H., Feuer, E., Cronin, K. SEER Cancer Statistics Review, 1975–2013. Bethesda, MD: National Cancer Institute; 2016.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2015; 65(1):5–29. [PubMed: 25559415]
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, Forman D, Bray F. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2012; 49(6):1374–403.
5. Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, Amso NN, Apostolidou S, Benjamin E, Cruickshank D, Crump DN, Davies SK, Dawnay A, Dobbs S, Fletcher G, Ford J, Godfrey K, Gunu R, Habib M, Hallett R, Herod J, Jenkins H, Karpinskyj C, Leeson S, Lewis SJ, Liston WR, Lopes A, Mould T, Murdoch J, Oram D, Rabideau DJ, Reynolds K, Scott I, Seif MW, Sharma A, Singh N, Taylor J, Warburton F, Widschwendter M, Williamson K, Woolas R, Fallowfield L, McGuire AJ, Campbell S, Parmar M, Skates SJ. Ovarian cancer screening and

mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): A randomised controlled trial. *Lancet*. 2016

6. Huang T, Tworoger SS, Hecht JL, Rice MS, Sood AK, Kubzansky LD, Poole EM. Association of ovarian tumor beta2-adrenergic receptor status with ovarian cancer risk factors and survival. *Cancer Epidemiol Biomarkers Prev*. 2016
7. Thaker PH, Han LY, Kamat AA, Arevalo JM, Takahashi R, Lu C, Jennings NB, Armaiz-Pena G, Bankson JA, Ravoori M, Merritt WM, Lin YG, Mangala LS, Kim TJ, Coleman RL, Landen CN, Li Y, Felix E, Sanguino AM, Newman RA, Lloyd M, Gershenson DM, Kundra V, Lopez-Berestein G, Lutgendorf SK, Cole SW, Sood AK. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med*. 2006; 12(8):939–44. [PubMed: 16862152]
8. Thaker PH, Sood AK, Ramondetta LM. Importance of adrenergic pathways in women's cancers. *Cancer Biomark*. 2013; 13(3):145–54. [PubMed: 23912486]
9. Thaker PH, Lutgendorf SK, Sood AK. The neuroendocrine impact of chronic stress on cancer. *Cell Cycle*. 2007; 6(4):430–3. [PubMed: 17312398]
10. Thaker PH, Sood AK. Neuroendocrine influences on cancer biology. *Semin Cancer Biol*. 2008; 18(3):164–70. [PubMed: 18201896]
11. Lutgendorf SK, Sood AK, Anderson B, McGinn S, Maiseri H, Dao M, Sorosky JI, De Geest K, Ritchie J, Lubaroff DM. Social support, psychological distress, and natural killer cell activity in ovarian cancer. *J Clin Oncol*. 2005; 23(28):7105–13. [PubMed: 16192594]
12. Walburn J, Vedhara K, Hankins M, Rixon L, Weinman J. Psychological stress and wound healing in humans: A systematic review and meta-analysis. *J Psychosom Res*. 2009; 67(3):253–71. [PubMed: 19686881]
13. Klein WM, Bloch M, Hesse BW, McDonald PG, Nebeling L, O'Connell ME, Riley WT, Taplin SH, Tesaro G. Behavioral research in cancer prevention and control: a look to the future. *Am J Prev Med*. 2014; 46(3):303–11. [PubMed: 24512871]
14. Lutgendorf SK, Lamkin DM, Jennings NB, Arevalo JM, Penedo F, DeGeest K, Langley RR, Lucci JA 3rd, Cole SW, Lubaroff DM, Sood AK. Biobehavioral influences on matrix metalloproteinase expression in ovarian carcinoma. *Clin Cancer Res*. 2008; 14(21):6839–46. [PubMed: 18980978]
15. Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. *Lancet Oncol*. 2004; 5(10):617–25. [PubMed: 15465465]
16. Lutgendorf SK, De Geest K, Bender D, Ahmed A, Goodheart MJ, Dahmouch L, Zimmerman MB, Penedo FJ, Lucci JA 3rd, Ganjei-Azar P, Thaker PH, Mendez L, Lubaroff DM, Slavich GM, Cole SW, Sood AK. Social influences on clinical outcomes of patients with ovarian cancer. *J Clin Oncol*. 2012; 30(23):2885–90. [PubMed: 22802321]
17. Huang T, Poole EM, Okereke OI, Kubzansky LD, Eliassen AH, Sood AK, Wang M, Tworoger SS. Depression and risk of epithelial ovarian cancer: Results from two large prospective cohort studies. *Gynecol Oncol*. 2015; 139(3):481–6. [PubMed: 26449316]
18. Berkman, LF., Kawachi, I., Theorell, T. Working conditions and health. In: Berkman, LF. Kawachi, I., Glymour, MM., editors. *Social Epidemiology*. 2. New York: Oxford University Press; 2014. p. 153–181.
19. Stansfeld S, Candy B. Psychosocial work environment and mental health: A meta-analytic review. *Scandinavian Journal of Work, Environment & Health*. 2006; 32(6):443–62.
20. Finne LB, Christensen JO, Knardahl S. Psychological and social work factors as predictors of mental distress and positive affect: A prospective, multilevel study. *PLoS One*. 2016; 11(3):e0152220. [PubMed: 27010369]
21. Alves MG, Hokerberg YH, Faerstein E. Trends and diversity in the empirical use of Karasek's demand-control model (job strain): A systematic review. *Rev Bras Epidemiol*. 2013; 16(1):125–36. [PubMed: 23681329]
22. Karasek, R., Theorell, T. *Healthy work: A stress, productivity and the reconstruction of working life*. New York: NY: Basic Books; 1990.
23. Huang Y, Xu S, Hua J, Zhu D, Liu C, Hu Y, Liu T, Xu D. Association between job strain and risk of incident stroke: A meta-analysis. *Neurology*. 2015
24. Kivimaki M, Kawachi I. Work stress as a risk factor for cardiovascular disease. *Curr Cardiol Rep*. 2015; 17(9):630. [PubMed: 26238744]

25. Virtanen M, Nyberg ST, Batty GD, Jokela M, Heikkilä K, Fransson EI, Alfredsson L, Bjorner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Elovainio M, Erbel R, Ferrie JE, Hamer M, Jockel KH, Kittel F, Knutsson A, Koskenvuo M, Koskinen A, Lunau T, Madsen IE, Nielsen ML, Nordin M, Oksanen T, Pahkin K, Pejtersen JH, Pentti J, Rugulies R, Salo P, Shipley MJ, Siegrist J, Steptoe A, Suominen SB, Theorell T, Toppinen-Tanner S, Vaananen A, Vahtera J, Westerholm PJ, Westerlund H, Slopen N, Kawachi I, Singh-Manoux A, Kivimäki M. Perceived job insecurity as a risk factor for incident coronary heart disease: Systematic review and meta-analysis. *BMJ*. 2013; 347:f4746. [PubMed: 23929894]
26. Eller NH, Netterstrom B, Gynzelberg F, Kristensen TS, Nielsen F, Steptoe A, Theorell T. Work-related psychosocial factors and the development of ischemic heart disease: A systematic review. *Cardiol Rev*. 2009; 17(2):83–97. [PubMed: 19367150]
27. Heikkilä K, Nyberg ST, Theorell T, Fransson EI, Alfredsson L, Bjorner JB, Bonenfant S, Borritz M, Bouillon K, Burr H, Dragano N, Geuskens GA, Goldberg M, Hamer M, Hoofman WE, Houtman IL, Joensuu M, Knutsson A, Koskenvuo M, Koskinen A, Kouvonen A, Madsen IE, Magnusson Hanson LL, Marmot MG, Nielsen ML, Nordin M, Oksanen T, Pentti J, Salo P, Rugulies R, Steptoe A, Suominen S, Vahtera J, Virtanen M, Vaananen A, Westerholm P, Westerlund H, Zins M, Ferrie JE, Singh-Manoux A, Batty GD, Kivimäki M. Work stress and risk of cancer: Meta-analysis of 5700 incident cancer events in 116,000 European men and women. *BMJ*. 2013; 346:f165. [PubMed: 23393080]
28. Achat H, Kawachi I, Byrne C, Hankinson S, Colditz G. A prospective study of job strain and risk of breast cancer. *Int J Epidemiol*. 2000; 29(4):622–8. [PubMed: 10922337]
29. Schernhammer ES, Hankinson SE, Rosner B, Kroenke CH, Willett WC, Colditz GA, Kawachi I. Job stress and breast cancer risk: The Nurses' Health Study. *Am J Epidemiol*. 2004; 160(11): 1079–86. [PubMed: 15561987]
30. Kuper H, Yang L, Theorell T, Weiderpass E. Job strain and risk of breast cancer. *Epidemiology*. 2007; 18(6):764–8. [PubMed: 17786125]
31. Blanc-Lapierre A, Rousseau MC, Weiss D, El-Zein M, Siemiatycki J, Parent ME. Lifetime report of perceived stress at work and cancer among men: A case-control study in Montreal, Canada. *Prev Med*. 2017; 96:28–35. [PubMed: 27923666]
32. Jansson C, Jeding K, Lagergren J. Job strain and risk of esophageal and cardia cancers. *Cancer Epidemiol*. 2009; 33(6):473–5. [PubMed: 19926547]
33. Willett WC, Green A, Stampfer MJ, Speizer FE, Colditz GA, Rosner B, Monson RR, Stason W, Hennekens CH. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med*. 1987; 317(21):1303–9. [PubMed: 3683458]
34. Camargo CA Jr, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Archives of Internal Medicine*. 1999; 159(21):2582–8. [PubMed: 10573048]
35. Bao Y, Bertola ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, Chavarro JE. Origin, methods, and evolution of the three Nurses' Health Studies. *Am J Public Health*. 2016; 106(9): 1573–81. [PubMed: 27459450]
36. NCI Cohort Consortium. Northern Sweden Health and Disease Study. 2016. Available at: <https://epi.grants.cancer.gov/Consortia/members/northsweden.html>
37. Weinehall L, Hallgren CG, Westman G, Janlert U, Wall S. Reduction of selection bias in primary prevention of cardiovascular disease through involvement of primary health care. *Scand J Prim Health Care*. 1998; 16(3):171–6. [PubMed: 9800231]
38. Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R. Plasma insulin-like growth factor 1, insulin-like growth factor binding protein 3, and risk of colorectal cancer: A prospective study in northern Sweden. *Gut*. 2002; 50(5):642–6. [PubMed: 11950809]
39. Karasek RA, Theorell T, Schwartz JE, Schnall PL, Pieper CF, Michela JL. Job characteristics in relation to the prevalence of myocardial infarction in the US Health Examination Survey (HES) and the Health and Nutrition Examination Survey (HANES). *Am J Public Health*. 1988; 78(8): 910–8. [PubMed: 3389427]
40. Landsbergis PA, Schnall PL, Warren K, Pickering TG, Schwartz JE. Association between ambulatory blood pressure and alternative formulations of job strain. *Scand J Work Environ Health*. 1994; 20(5):349–63. [PubMed: 7863299]

41. Theorell T, Perski A, Akerstedt T, Sigala F, Ahlberg-Hulten G, Svensson J, Eneroth P. Changes in job strain in relation to changes in physiological state: A longitudinal study. *Scand J Work Environ Health*. 1988; 14(3):189–96. [PubMed: 3393855]
42. Karasek R, Choi B, Ostergren PO, Ferrario M, De Smet P. Testing two methods to create comparable scale scores between the Job Content Questionnaire (JCQ) and JCQ-like questionnaires in the European JACE Study. *Int J Behav Med*. 2007; 14(4):189–201. [PubMed: 18001234]
43. Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care*. 1992; 30(6):473–83. [PubMed: 1593914]
44. Tworoger SS, Hecht JL, Giovannucci E, Hankinson SE. Intake of folate and related nutrients in relation to risk of epithelial ovarian cancer. *Am J Epidemiol*. 2006; 163(12):1101–11. [PubMed: 16554344]
45. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994; 140(11):1016–9. [PubMed: 7985649]
46. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: A sample survey for year 1998. *Acta Oncol*. 2009; 48(1):27–33. [PubMed: 18767000]
47. Sveriges officiella statistik. Dödsorsaksstatistik: Historik, produktionsmetoder och tillförlitlighet Socialstyrelsen. 2010.
48. Ji J, Forsti A, Sundquist J, Lenner P, Hemminki K. Survival in ovarian cancer patients by histology and family history. *Acta Oncol*. 2008; 47(6):1133–9. [PubMed: 18607880]
49. Chandola T, Heraclides A, Kumari M. Psychophysiological biomarkers of workplace stressors. *Neurosci Biobehav Rev*. 2010; 35(1):51–7. [PubMed: 19914288]
50. Hansen AM, Larsen AD, Rugulies R, Garde AH, Knudsen LE. A review of the effect of the psychosocial working environment on physiological changes in blood and urine. *Basic Clin Pharmacol Toxicol*. 2009; 105(2):73–83. [PubMed: 19563453]
51. Koenigsberg HW, Teicher MH, Mitropoulou V, Navalta C, New AS, Trestman R, Siever LJ. 24-h Monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. *J Psychiatr Res*. 2004; 38(5):503–11. [PubMed: 15380401]
52. Roy A, Pickar D, De Jong J, Karoum F, Linnoila M. Norepinephrine and its metabolites in cerebrospinal fluid, plasma, and urine: Relationship to hypothalamic-pituitary-adrenal axis function in depression. *Arch Gen Psychiatry*. 1988; 45(9):849–57. [PubMed: 3415426]
53. Antai D, Oke A, Braithwaite P, Anthony DS. A ‘balanced’ life: Work-life balance and sickness absence in four nordic countries. *Int J Occup Environ Med*. 2015; 6(4):205–22. [PubMed: 26498049]
54. Kivimäki M, Jokela M, Nyberg ST, Singh-Manoux A, Fransson EI, Alfredsson L, Björner JB, Borritz M, Burr H, Casini A, Clays E, De Bacquer D, Dragano N, Erbel R, Geuskens GA, Hamer M, Hoofman WE, Houtman IL, Jockel KH, Kittel F, Knutsson A, Koskenvuo M, Lunau T, Madsen IE, Nielsen ML, Nordin M, Oksanen T, Pejtersen JH, Pentti J, Rugulies R, Salo P, Shipley MJ, Siegrist J, Steptoe A, Suominen SB, Theorell T, Vahtera J, Westerholm PJ, Westerlund H, O’Reilly D, Kumari M, Batty GD, Ferrie JE, Virtanen M. Long working hours and risk of coronary heart disease and stroke: A systematic review and meta-analysis of published and unpublished data for 603,838 individuals. *Lancet*. 2015; 386(10005):1739–46. [PubMed: 26298822]
55. Burgard SA, Lin KY. Bad jobs, bad health? How work and working conditions contribute to health disparities. *Am Behav Sci*. 2013; 57(8)
56. Williams G, Dean P, Williams E. Do nurses really care? Confirming the stereotype with a case control study. *Br J Nurs*. 2009; 18(3):162–5. [PubMed: 19223800]
57. Erenstein CF, McCaffrey R. How healthcare work environments influence nurse retention. *Holist Nurs Pract*. 2007; 21(6):303–7. [PubMed: 17978634]
58. Trudel-Fitzgerald C, Chen Y, Singh A, Okereke OI, Kubzansky LD. Psychiatric, psychological, and social determinants of health in the Nurses’ Health Study cohorts. *Am J Public Health*. 2016; 106(9):1644–9. [PubMed: 27459447]

Table 1

Age-standardized Characteristics of Participants at Baseline

	<i>Job strain categories</i>				<i>p-value^a</i>
	Low demand High control ("Low Strain") (n=4,744; 14.9%)	Low demand Low control ("Passive") (n=9,178; 28.9%)	High demand High control ("Active") (n=7,755; 24.4%)	High demand Low control ("High Strain") (n=10,077; 31.7%)	
NHS (1992; N=31,754)					
Age, mean (SD) ^b	55.3 (6.0)	56.7 (6.4)	54.1 (5.5)	55.0 (5.9)	<0.0001
Marital status (married), %	80.3	82.6	79.5	80.1	0.02
Census tract income, mean (SD)	66360.8 (25812.7)	65654.5 (25050.1)	66446.0 (25082.5)	64917.9 (24085.1)	0.0002
Ever use OC, %	61.4	59.1	60.5	59.3	0.09
Ever use HT ^c , %	49.0	45.5	47.7	47.0	0.73
Ever pregnant, %	94.8	95.1	94.7	95.1	0.52
Tubal ligation, %	22.9	22.0	21.9	22.0	0.44
Post-menopausal, %	61.5	61.6	60.2	60.4	0.01
Family history of breast or ovarian cancer, %	13.9	13.3	13.7	13.9	0.65
BMI (kg/m ²), mean (SD)	26.2 (5.1)	26.2 (5.1)	26.2 (5.0)	26.1 (5.1)	0.82
Never smoker, %	43.8	44.4	43.3	43.8	0.47
NHSII (1993; N=74,261)	(n=11,139; 15.0%)	(n=15,521; 20.9%)	(n=23,568; 31.7%)	(n=24,033; 32.4%)	
Age, mean (SD) ^b	38.9 (4.6)	38.4 (4.6)	38.5 (4.7)	38.1 (4.6)	<0.0001
Marital status (married), %	91.0	92.0	90.1	90.9	0.03
Census tract income, mean (SD)	61910.9 (22628.6)	62007.9 (22069.4)	62387.0 (22530.0)	61641.3 (21676.3)	0.01
Ever use OC, %	86.4	84.2	86.2	84.7	0.03
Ever use HT ^c , %	79.7	70.9	72.9	70.0	0.08
Ever pregnant, %	76.5	79.8	73.2	75.3	<0.0001
Tubal ligation, %	21.3	22.2	20.2	20.4	0.0002
Post-menopausal, %	1.1	1.1	1.1	1.2	0.56
Family history of breast or ovarian cancer, %	7.3	7.3	7.8	7.5	0.25
BMI (kg/m ²), mean (SD)	25.2 (5.7)	25.1 (5.6)	25.4 (5.8)	25.4 (5.9)	<0.0001
Never smoker, %	65.5	66.6	64.7	64.9	0.01
NSHDS (N_{controls}=94)	(n=12; 12.8%)	(n=31; 33.0%)	(n=28; 30.0%)	(n=23; 24.4%)	

	<i>Job strain categories</i>				<i>p-value^a</i>
	Low demand High control ("Low Strain") (n=4,744; 14.9%)	Low demand Low control ("Passive") (n=9,178; 28.9%)	High demand High control ("Active") (n=7,755; 24.4%)	High demand Low control ("High Strain") (n=10,077; 31.7%)	
NHS (1992; N=31,754)					
Age, mean (SD) ^b	52.6 (7.5)	50.5 (8.7)	47.1 (7.3)	52.6 (7.6)	0.06
Marital status (married), %	93.8	94.0	68.7	87.0	0.002
Education level (college), %	49.3	54.3	54.0	38.3	0.36
Ever used OC, %	78.7	38.9	65.6	35.1	0.14
Ever used HT ^c , %	0.0	17.2	8.1	9.4	0.43
Ever pregnant, %	100.0	70.1	78.1	66.5	0.07
Tubal ligation, %	8.9	0.0	5.3	0.0	1.00
Post-menopausal, %	40.0	41.2	38.2	52.6	0.58
Family history of breast or ovarian cancer, %	17.8	16.6	7.7	0.0	<0.0001
BMI (kg/m ²), mean (SD)	25.2 (3.2)	26.8 (4.7)	24.5 (3.7)	24.9 (3.7)	0.02
Never smokers, %	36.2	54.6	58.9	41.3	0.31

SD=Standard deviation; OC=Oral contraceptive; HT= Hormone therapy; BMI=Body mass index.

^aExact logistic regression models were used for marital status, ever used HT, tubal ligation and family history of breast or ovarian cancer variables in the NSHDS cohort given the small number of participants in some cells, while ANOVA and logistic regressions models were used for all other variables in the three cohorts.

^bValues are means(SD) or percentages and are standardized to the age distribution of the study population (age value is not age adjusted).

^cAmong post-menopausal women.

Table 2

Multivariate Models Assessing the Role of Stress-related Work Characteristics on OvCA Risk

<i>Cox regression models among NHS cohorts (N = 106,014; 294 cases)</i>				
	Model 1 ^a		Model 2 ^b	
<i>Job Strain^c (4 categories)</i>	HR	95% CI	HR	95% CI
Low Strain (n=15,678; 41 cases)	1.00	ref.	1.00	ref.
Passive (n=23,209; 83 cases)	1.53	1.04, 2.25	1.55	1.05, 2.28
Active (n=32,065; 91 cases)	1.28	0.88, 1.86	1.27	0.87, 1.85
High Strain (n=35,062; 79 cases)	1.07	0.73, 1.58	1.08	0.74, 1.59
<i>Control subscale (tertiles)</i>				
High control (n=37,698; 96 cases)	1.00	ref.	1.00	ref.
Moderate control (n=33,814; 92 cases)	1.11	0.83, 1.48	1.12	0.83, 1.49
Low control (n=34,502; 106 cases)	1.30	0.98, 1.72	1.31	0.99, 1.74
<i>Demand subscale (tertiles)</i>				
Low demand (n=23,457; 71 cases)	1.00	ref.	1.00	ref.
Moderate demand (n=31,296; 74 cases)	0.64	0.47, 0.87	0.64	0.47, 0.88
High demand (n=51,261; 129 cases)	0.75	0.57, 0.99	0.74	0.56, 0.98
<i>Conditional logistic regression models among the NSHDS cohort (N = 196; 102 cases)</i>				
	Model 1		Model 2	
<i>Job Strain (4 categories)</i>	OR	95% CI	OR	95% CI
Low Strain (n=23; 11 cases)	1.00	ref.	1.00	ref.
Passive (n=63; 32 cases)	0.43	0.06, 3.36	0.36	0.04, 3.40
Active (n=65; 37 cases)	1.12	0.14, 7.24	1.23	0.16, 9.68
High Strain (n=45; 22 cases)	0.25	0.02, 2.56	0.46	0.04, 5.39
<i>Control subscale (tertiles)</i>				
High control (n=82; 45 cases)	1.00	ref.	1.00	ref.
Moderate control (n=60; 28 cases)	0.23	0.04, 1.21	0.21	0.04, 1.26
Low control (n=54; 29 cases)	0.67	0.12, 3.64	0.54	0.10, 2.95
<i>Demand subscale (tertiles)</i>				
Low demand (n=86; 43 cases)	1.00	ref.	1.00	ref.
Moderate demand (n=65; 34 cases)	0.83	0.23, 2.96	1.39	0.28, 6.83
High demand (n=45; 25 cases)	0.97	0.28, 3.34	1.80	0.46, 7.13
<i>Meta-analyses with random effects models and fully-adjusted coefficients</i>				
<i>Job Strain (4 categories)</i>	RR	95% CI	Q statistic (heterogeneity)	P-value
Passive	1.16	0.37, 3.60	1.56	0.21
Active	1.27	0.87, 1.84	0.00	0.97
High Strain	1.06	0.72, 1.55	0.45	0.50
<i>Control subscale (tertiles)</i>				
Moderate control	0.62	0.13, 2.92	3.23	0.07
Low control	1.27	0.92, 1.76	1.02	0.31
<i>Demand subscale (tertiles)</i>				

Meta-analyses with random effects models and fully-adjusted coefficients

<i>Job Strain (4 categories)</i>	RR	95% CI	Q statistic (heterogeneity)	P-value
Moderate demand	0.66	0.49, 0.90	0.86	0.35
High demand	0.89	0.44, 1.77	1.53	0.22

^a Model 1: age, marital status, income (NHS cohorts) or education (NSHDS), OC use, ever pregnant, tubal ligation (NHS only), familial history of breast or ovarian cancer, menopausal status, HT use (NHS only)

^b Model 2: Model 1 + BMI, alcohol, physical activity, caffeine (NHS cohorts only), calories (NHS cohorts only), smoking

^c Low Strain=Low Demand & High Control; Passive=Low Demand & Low Control; Active=High Demand & High Control; High Strain=High Demand & Low Control