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Depression and Risk of Epithelial Ovarian Cancer: Results from Two Large Prospective Cohort Studies

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Abstract

Objectives—While emerging evidence supports a possible link between depression and ovarian cancer progression, no prospective studies have explored the association with ovarian cancer risk.

Methods—We prospectively followed 77 451 women from the Nurses' Health Study (1992-2010) and 106 452 women from the Nurses' Health Study II (1993-2011). Depression was defined as having one or more of the following: a 5-item Mental Health Index (MHI-5) score≤52, antidepressant use, or physician-diagnosed depression. Multivariate-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between depression and incident ovarian cancer.

Results—We documented 698 incident cases of epithelial ovarian cancer during follow-up. In multivariable analyses, depression assessed 2-4 years before cancer diagnosis was associated with a modestly higher incidence of ovarian cancer (HR=1.30, 95% CI1.05-1.60). Compared to women with persistent negative depression status, the adjusted HRs were 1.34 (95% CI 1.01-1.76) for women with persistent positive depression status and 1.28 (95% CI 0.88-1.85) for women with

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worsening depression status over follow-up. The association did not appear to vary by ovarian cancer risk factors or tumor characteristics.

Conclusions—Our findings suggest that depression may be associated with a modestly increased risk of ovarian cancer. Given the relatively high prevalence of depression in women, future work in larger prospective human studies is needed to confirm our results.

Keywords

depression; ovarian cancer; chronic stress; repeated measures; latency period; etiology

Introduction

Depression is a common public health problem that has been linked with a number of chronic health outcomes, including coronary heart disease, diabetes and arthritis [1].Further, depression can lead to neuroendocrine, immunological and behavioral changes that have been implicated in several important carcinogenic pathways. For example, depression has been associated with elevated inflammation, metabolic dysfunction and increased obesity[2, 3], and can lead to unhealthy behaviors, such as smoking, physical inactivity and excess calorie intake. Although these factors are well established in the etiology of many cancers, previous prospective studies on depression and cancer incidence were inconsistent, reporting positive[4-6] or null findings[7-11]. These studies varied by sample size, depression assessment, and follow-up period. Importantly, most studies focused on total incidence of cancer, even though there are clearly different risk factors for various cancer sites, and were unable to examine rare tumors, such as ovarian cancer.

Ovarian cancer is the fifth leading cause of cancer death in US women [12].Recent experimental evidence suggests that dysregulated stress hormones such as cortisol and catecholamines, which have been observed in depressed patients, may promote growth and progression of ovarian cancer via stress-mediated pathways[13, 14].Several observational studies in ovarian cancer patients also showed a poorer prognosis and shorter survival associated with higher levels of depression or stress [15-18].However, whether depression is associated with an increased risk of ovarian cancer remains unknown. Prospective studies are needed to evaluate this association, as they may provide greater insight into ovarian cancer etiology and prevention strategies.

In this study, we examined whether depression was associated with risk of incident epithelial ovarian cancer during 18 years of follow-up in two large prospective cohorts, considering the latency between timing of depression assessment and ovarian cancer diagnosis. We also used repeated depression assessments to evaluate change and persistence of depression in relation to ovarian cancer risk.

Materials and Methods

Study population

We used data from two on-going large prospective cohorts: the Nurses' Health Study (NHS), established in 1976 among 121,700 US female registered nurses aged 30-55, and the

Nurses' Health Study II (NHSII), initiated in 1989 among 116,430 nurses aged 25-42. Participating women in both cohorts completed a baseline questionnaire regarding their medical history, health conditions and lifestyle factors, and updated their information on exposure, disease diagnoses and important covariatesonbiennial follow-up questionnaires. The study was approved by the institutional review boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health.

Depression assessment

Several depression-related measures, including the Mental Health Index, antidepressant medication use, and self-reported physician-diagnosed depression, were assessed in both cohorts. Depressive symptoms, using the 5-item Mental Health Index (MHI-5) from the Short-Form 36 Health Status Survey[19], were assessed in 1992, 1996, 2000 in NHS and in 1993, 1997, 2001 in NHSII. Items on this scale asked women how much of the time during the past 4 weeks (all, most, good bit, some, little, or none) they felt nervous, felt so down that nothing could cheer them up, felt calm and peaceful, felt down and blue, or felt happy. Responses were scored from 0 to 100, with lower scores indicating higher depressive symptoms. Prior work has shown that a MHI-5 score≤52 was highly discriminant of clinically-diagnosed depression [20]. MHI-5 was used as an indicator for women's depressive symptoms during the 4-year period after each assessment. Regular antidepressant use in past two years was first reported in 1996 in NHS and in 1993 in NHSII, and was updated biennially (except 1995 in NHSII). Antidepressant medications included selective serotonin reuptake inhibitors (e.g., Prozac, Zoloft, Paxil, Celexa) and other antidepressants (e.g., Elavil, Tofranil, Pamelor). Since 2000 in NHS and 2003 in NHSII, physician-diagnosed depression was documented biennially by self-report on the questionnaire. A diagnosis made during past two years was used to indicate current physician-diagnosed depression status.

Assessment of ovarian cancer and death

Pathology reports and related medical records were obtained for all incident epithelial ovarian cancer cases reported on each biennial questionnaire. A gynecologic pathologist blinded to women's exposure status reviewed the pathology reports to confirm the diagnosis, as well as to identify tumor characteristics including morphology, stage, histology, and invasiveness. Deaths of cohort members and the related cause of death were identified by family members, the US Postal Service, or the National Death Index, which captures 98% of all deaths in this cohort. In a subset of 215 ovarian cancer cases, concordance between reviews of pathology records and surgical pathology slides was 98% for invasiveness and 83% for histologic type [21].

Statistical analysis

To maximize statistical power, our primary analysis included women who had information on at least one of the three depression measures during follow-up since 1992 in NHS and 1993 in NHSII. Women who died (NHS: 5,250; NHSII: 244), or had bilateral oophorectomy(NHS: 22,318; NHSII: 5,208), menopause due to pelvic irradiation (NHS: 417; NHSII: 92), ordiagnosis of cancer other than non-melanoma skin cancer (NHS: 6,343; NHSII: 1,152) before their first report of depression-related measuresor had no assessment

on depression (NHS: 9,921; NHSII: 3282) were excluded, resulting in 77,451 NHS women and 106,452 NHSII women in the analysis. We excluded women with bilateral oophorectomy because they were theoretically not at risk for ovarian cancer. We also excluded women with pelvic irradiation because ovarian cancer resulting from irradiation had a different etiology.

Women were considered to have depression if they met one or more of the following criteria: MHI-5≤52, antidepressant use, or current physician-diagnosed depression, whenever the information was available from the questionnaire. This definition of depression previously has been associated with increased risk of stroke, diabetes and obesity in the cohort[22-24]. Secondarily, we examined the association with MHI-5 and antidepressant use separately; we had limited power to assess physician-diagnosed depression alone. For MHI-5, we further evaluated potential dose-response relationship by categorizing the score into four groups (0-52, 53-75, 76-85, and 86-100) [6]. We also evaluated whether antidepressant use may modify the association between depression and ovarian cancer.

Person-time for each participant was calculated from the time of the first report of depression-related measures to the date of ovarian or any other cancer diagnosis (except non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (NHS: June 2010; NHSII: June 2011), whichever occurred first. Women only contributed person-time for follow-up periods in which they provided responses for at least one of the depression measures. We used Cox proportional hazards models with time-varying variables to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between depression and ovarian cancer. The proportional hazards assumption was verified by testing interaction terms with age and calendar time. To address the possibility that preclinical symptoms of ovarian cancer may influence depression status, we introduced a latency of 2-4 years between exposure assessment and disease diagnosis. For example, in the NHSII, we examine depression status in 1993 with diagnoses in 1995-1997, depression status in 1995 with diagnoses in 1997-1999, and so on.

We first fit the model stratified by age and calendar time in months. Next, we included ovarian cancer risk factors in the model, including menopausal status, parity, duration of oral contraceptive (OC) use, duration of postmenopausal hormone use (PMH) by type, history of tubal ligation, history of hysterectomy, and family history of breast cancer or ovarian cancer. To explore whether the observed association may be explained bybehavioral changes following depression,we further adjusted for potential mediating lifestyle factors that could be altered by depression, including body mass index (BMI), physical activity, smoking, intake of caffeine and lactose. These covariates were used as time-varying variables in the analysis. Analyses were conducted separately in each cohort and heterogeneity was assessed by random-effects meta-analysis. Since no heterogeneity was observed, we combined the data and additionally stratified by cohort in the model.

We performed similar analyses to examine change and persistence of depression in relation to ovarian cancer risk. By comparing depression status between the current versus the previous questionnaire assessment using our primary definition, women were divided into

four groups: 1) persistent negative depression status (i.e., did not meet the definition on the current or past questionnaires), 2) persistent positive depression status (i.e., met the depression definition on the current and past questionnaires), 3) improved depression status (i.e., met the depression definition on the past but not the current questionnaire), 4) worsening depression status (i.e., met the depression definition on the current but not the past questionnaire). Burden of depression was defined as the proportion of questionnaires meeting the primary depression definition (none, 0-1/3, 1/3-2/3, >2/3), restricted to women with ≥3 depression assessments.

To evaluate whether the association was stronger for high-risk women,we conducted stratified analyses by age, menopausal status, PMH use, OC use, and family history of breast or ovarian cancer; a likelihood ratio test was used to evaluate the significance of interactions. We also restricted the analysis to women who did not use beta-blocker medications, as beta-blockers may inhibit the stress-related pathways mediated through β_2-adrenergic receptor [14].Additional analyses used competing risks Cox model [25] to examine associations by histologic subtype (serous/poorly differentiated versus non-serous) and by tumor aggressiveness (fatal within 3 years of diagnosis or not).

Several sensitivity analyses wereperformed, including: 1)starting the follow-up in 2000 for NHS and 2003 for NHSII, when all three depression measures were available simultaneously; 2) evaluating depression assessed 4-6 years before diagnosis; and 3) considering baseline depression status (i.e., the first reported depression status). All analyses were conducted in SAS 9.3 (Cary, NC).

Results

During 18 years of follow-up, 698 incident ovarian cancer cases were identified among 183,903 women with 2,430,454 person-years of follow-up.In 2002, the midpoint of follow-up, 12.6% of NHS women had depression using the primary definition, while the prevalence was 23.3% among NHSII women in 2003. In both cohorts, women with depression were more likely to have history of tubal ligation or hysterectomy, use OC, PMH or beta-blockers, smoke cigarettes, be obese, and be physically inactive (Table 1).

The association between depression and ovarian cancer was similar across the two cohorts ($P_{heterogeneity}$>0.73). In pooled analyses adjusted for ovarian cancer risk factors, depression assessed 2-4 years before diagnosis was associated with a modestly increasedrisk of ovarian cancer (HR=1.30; 95% CI: 1.05, 1.60; Table 2). Further adjustment of lifestyle factors, particularly BMI, modestly attenuated the association, but the result remained statistically significant (HR=1.26; 95% CI: 1.02, 1.56). When examining the association with MHI-5 and antidepressant use separately, the multivariable HRs (95% CIs) were 1.33 (0.99, 1.79) for MHI-5 ≤52 versus >52 and 1.15 (0.88, 1.51) for current antidepressant use versus not. Further, we did not observe a linear dose-response association between MHI-5 and ovarian cancer risk.The increased risk was only observed among women with severe (i.e., MHI-5≤52) but not moderate (i.e., MHI-5 between 53-75) depressive symptoms (data not shown). When stratifying depression status by antidepressant use, the multivariable HR

(95% CI) was 1.23 (0.93, 1.61) for women with depression who had antidepressant use, and 1.52 (1.03, 2.22) for women with depression who did not report antidepressant use.

Compared to women with persistent negative depression status, we observed an increased risk of ovarian cancer among women with persistent positive depression status (HR=1.34; 95% CI: 1.01, 1.76) and a suggestively increased risk for worsening depression status (HR=1.28; 95% CI: 0.88, 1.85), whereas women with improved depression status were not at higher risk (HR=0.88; 95% CI: 0.54, 1.41; Table 3). Greater burden of depression also was associated with a suggestively elevated risk of ovarian cancer, with women meeting the depression criteria more than two thirds of the time having the highest risk (HR=1.38; 95% CI: 0.98, 1.94; P_{trend}=0.06).

We did not observe a significant difference in the association by ovarian cancer risk factors (data not shown), although the association was suggestively stronger among younger women (HR=1.56; 95% CI: 1.12, 2.17 for <55 yrs; HR=1.18; 95% CI: 0.84, 1.65 for 55-70 yrs; HR=1.10; 95% CI: 0.69, 1.73 for >70 yrs) or premenopausal women (HR=1.59; 95% CI: 1.10, 2.29 for premenopausal women; HR=1.18; 95% CI: 0.91, 1.52 for postmenopausal women).When restricted to beta-blocker non-users, the result was similar to the overall association (HR=1.34; 95% CI: 1.08, 1.67).The associations also were similar for serous versus non-serous tumors and for rapidly fatal versus less aggressive tumors (data not shown).

Sensitivity analysis restricted to later follow-up cycles with all three depression measures available showed a suggestively stronger association (HR=1.51; 95% CI: 1.10, 2.07; Supplementary Table 1). Compared to the association with depression assessed 2-4 years before ovarian cancer diagnosis, the positive association with depression assessed 4-6 years before diagnosis were slightly weaker and did not reach statistical significance (HR=1.22; 95% CI: 0.97, 1.53), whereas baseline depression status was not associated with ovarian cancer risk (HR=0.97; 95% CI: 0.76, 1.24; Supplementary Table 2).

Discussion

In this pooled analysis of two prospective cohort studies, we observed a modestly increased risk of ovarian cancer among women with depression. Women with persistent positive depression status also had a higher risk of ovarian cancer than women intermittently positive or persistently negative for depression. The strongest association was observed for depression assessed 2-4 years before diagnosis, consistent with experimental findings that stress is a promoting factor at later stages of ovarian carcinogenesis.

Our estimates of depression prevalence were similar to previous reports, which showed almost doubled prevalence in younger versus older women[26]. Despite lack of prior studies on depression and ovarian cancer risk specifically, a number of large-scale, prospective studies have evaluated depression with total cancer incidence or other cancer sites, producing mixed results. Intriguingly, positive associations were generally observed in longitudinal studies with repeated assessment of depression, similar to ours[4-6]. In contrast, studies using a single baseline depression assessment were more likely to report null

associations[7-9], and baseline depression status was also not associated with ovarian cancer risk in our study. Although the validity has been questioned [27], two meta-analyses suggest a positive association between depression and cancer risk [28, 29], particularly in cohort studies with larger sample size and longer follow-up. Collectively, these observations highlight the importance of using repeated depression measures to consider remission/relapse of depression over time and etiologically relevant induction period in cancer development.

Depression may be positively associated with ovarian cancer risk through a variety of mechanisms. First, individuals with depression are usually under chronic stressand have impaired immune function, with increased genomic instability and reduced immune surveillance[30]. Stress also impairs wound healing[31], which may be important in the context of post-ovulatory wound repair, as accumulations of deleterious mutations by the ovulation-induced wounds on ovarian surface epithelium have been proposed to lead to neoplasia[32]. Second, depression may promoteadipogenesis and systemic inflammation[2, 3], both of which have been associated with increased ovarian cancer risk [33, 34].Third, depression could lead to alterations in behaviors, such as smoking, physical activity and diet, which may play a role in mediating the effect, although their associations with ovarian cancer are not conclusive and adjusting for these factors only modestly attenuated the association between depression and ovarian cancer risk.Some of these mechanisms may help explain the suggestively stronger association observed in younger and premenopausal women. For example, the mechanism via post-ovulatory wound healing is only relevant among premenopausal women, and BMI appears to have a stronger association with ovarian cancer in premenopausal women [33]. This may also be attributed to higher susceptibility to depression among women of reproductive age [35]. However, we cannot rule out the possibility that competing risks may have attenuated the associations in older women, given that depression and its comorbidities can cause premature mortality[1].Fourth, emergingevidence suggests that stress-induced dysregulation in glucocorticoids and catecholamines, which has been consistently observed in patients with depression[36, 37], can enhance ovarian tumor growth and progression [13, 14]. Although existing evidence has focused on progression and metastasis, it is possible that these stress-mediated signaling pathways are also important in ovarian cancer incidence. Additional studies are needed to understand the underlying mechanisms.

Interestingly, while there was a similar positive association with depressive symptoms assessed by MHI-5 alone, we did not observe a significantly increased risk of ovarian cancer with antidepressant use. This may be explained by the fact that antidepressants can be prescribed for women without depression to treat other conditions. It is also possible that antidepressant use may alleviate depressivesymptomsand reverse some of the neuroendocrine dysfunction, thereby reducing the impact of depression on ovarian cancer development. Further, we observed a higher risk among women with persisting or worsening depression, which could lead to prolonged exposure to abnormal stress hormone levels and chronically higher inflammation status [38].

The study strengths include the prospective design, large sample size, and long follow-up. Our depression definition combined three depression-related measures, which were

repeatedly queried in both cohorts. This allowed assessment of depression as a time-varying variable, as well as characterization of change and persistence. These exposure definitions may better reflect the episodic nature and severity of depression, compared to a single baseline measurement as considered in previous studies[39]. We were able to account for a number of detailed ovarian cancer risk factors and depression-related lifestyle factors in the analysis.

One limitation of the current study is the potential misclassification of depression status. As is the case in many large-scale epidemiologic studies, our measure of depression has not been clinically validated [40]. Rather, we utilized several self-reported measures: MHI-5≤52 may not exactly correspond to a clinical diagnosis; antidepressants are not prescribed for every diagnosed depression patient and are used to treat conditions other than depression; and depression is under-diagnosed by physicians[40]. However, excluding women who were defined as having depression solely based on antidepressant use (i.e., those that were more likely to use antidepressants to treat other conditions such as anxiety or chronic pain) resulted in a similar positive association (HR=1.28; 95% CI: 1.01, 1.62). Importantly, the combined definition enabled us to capture different aspects of depression and maximize our ability to identify women experiencing depression in some form. Also, this measure of depression has been associated with stroke, type 2 diabetes and obesity in the NHS/NHSII[22-24], suggesting that this measure provides important signals of mental health processes and their effects on physical health outcomes. Further, this non-differential misclassification may lead to underestimation of the true association. Of note, since not all depression-related measures were available on each questionnaire (e.g., physician-diagnosed depression was queried after 2000), the extent of non-differential misclassification may vary by cycle. However, the sensitivity analysis restricted to later follow-up periods with all three depression-related measures showed similar results, corroborating the robustness of our findings.

In summary, this study provides prospective evidence in humans that depression is associated with a modestly increased risk of ovarian cancer. Findings should be confirmed in other large cohorts with longitudinal assessment of depression, and extended by mechanistic studies to elucidate the underlying mechanisms. If replicated, our results suggest that interventions to treat women with depression may enrich current prevention strategies for ovarian cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research highlights

- This study includes 183,903 women from two prospective US cohorts with about 700 ovarian cancer cases.
- Depression assessed 2-4 years before cancer diagnosis was associated with about 30% increased risk of ovarian cancer.
- Women with persistent positive depression status had a higher risk of ovarian cancer.

Table 1

Age-standardized Characteristics of the Study Population at the Midpoint of Follow-up by Depression Status in the Nurses' Health Study (2002) and Nurses' Health Study II (2003)[a]

	Depression status[b]			
	Nurses' Health Study		Nurses' Health Study II	
	No	Yes	No	Yes
N	52,077	7,509	72,411	19,936
MHI-5	82.8 (10.3)[c]	64.3 (19.2)	78.6 (10.6)	59.0 (18.9)
Antidepressant use, %	0	72	0	65
Current physician-diagnosed depression, %	0	15	0	15
History of physician-diagnosed depression, %	2	42	3	45
Age, years	67.9 (7.1)	66.7 (7.2)	48.3 (4.7)	48.5 (4.6)
History of tubal ligation, %	21	23	21	24
History of hysterectomy, %	21	28	9	12
Family history of breast or ovarian cancer, %	18	19	12	13
Parous, %	95	95	84	82
Number of children in parous women	3.2 (1.5)	3.1 (1.4)	2.3 (0.9)	2.3 (0.9)
Ever OC use, %	49	54	76	84
Duration of OC use, months[d]	50.7 (46.2)	46.9 (44.0)	68.8 (62.3)	71.0 (62.7)
Postmenopausal, %	99	99	23	25
Estrogen-only PMH use, %[e]	16	22	5	5
Duration of estrogen-only PMH use, months[de]	103.5(83.5)	114.1(88.6)	3.6 (3.3)	4.0 (3.7)
Estrogen-progestin PMH use, %[e]	32	35	29	32
Duration of estrogen-progestin PMH use, months[de]	78.7 (50.5)	81.9 (52.3)	3.3 (2.5)	3.3 (2.7)
Caffeine, mg/day[f]	159.0 (160.9)	149.8 (154.6)	184.5 (169.8)	192.6 (172.2)
Lactose, g/day[f]	15.9 (12.3)	16.3 (12.7)	17.1 (12.8)	16.8 (12.8)
Beta blocker use, %	14	18	4	8
Current smokers, %	9	11	7	11

	Depression status[b]			
	Nurses' Health Study		Nurses' Health Study II	
Physical activity, MET-hour/week	17.8 (22.5)	14.1 (19.6)	21.9 (28.7)	18.1 (25.4)
BMI (kg/m^2)	26.7 (5.3)	27.7 (6.2)	26.6 (6.1)	28.3 (7.1)

[a] MHI-5 = 5-item Mental Health Index; OC = oral contraceptive; PMH = postmenopausal hormone; BMI = body mass index

[b] Defined as having one or more of the following: MHI-5≤52, antidepressant medication use or physician-diagnosed depression

[c] Mean (SD) unless noted as a percent

[d] Duration among ever users

[e] Among postmenopausal women

[f] Intake adjusted for total energy using the nutrient residual method

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Table 2

Hazard Ratio (HR) and 95% Confidence Interval (CI) for the Association Between Depression and Risk of Incident Epithelial Ovarian Cancer in the Nurses' Health Study (1992-2010) and Nurses' Health Study II (1993-2011)

Depression status[a]	Cases/person-years	Age-adjusted[b]	Adjusted for ovarian cancer risk factors[c] HR (95% CI)	Additionally adjusted for potential mediators[d]
Nurses' Health Study (n=484)				
No	423/837,087	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	61/93,577	1.32 (1.01, 1.73)	1.25 (0.96, 1.65)	1.23 (0.93, 1.61)
Nurses' Health Study II (n=214)				
No	166/1,247,499	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	48/252,293	1.40 (1.01, 1.94)	1.35 (0.98, 1.87)	1.30 (0.94, 1.81)
Pooled (n=698)				
No	589/2,084,585	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Yes	109/345,869	1.35 (1.10, 1.66)	1.30 (1.05, 1.60)	1.26 (1.02, 1.56)

[a] Defined as having one or more of the following: 5-item Mental Health Index≤52, antidepressant medication use or physician-diagnosed depression

[b] Stratified by age in months and calendar years, and additionally by cohort for pooled analysis

[c] Age-adjusted model plus menopausal status (premenopausal, postmenopausal), parity (nulliparous, 1, 2, 3, >3 children), duration of oral contraceptive use (never, <1, 1 to 5, >5 years), duration of postmenopausal hormone use by type (never, <5, 5 to 10, >10 years for estrogen only and estrogen plus progestin, separately), history of tubal ligation (yes, no), history of hysterectomy (yes, no), and family history of breast cancer or ovarian cancer (yes, no)

[d] Ovarian cancer risk factor model plus body mass index (<20, 20 to <25, 25 to <30, ≥30 kg/m^2), physical activity (<3, 3 to <9, 9 to <18, 18 to <27, ≥27 MET-h/week), smoking (never, past, current), caffeine intake (mg/d, in quintiles) and lactose intake (g/d, in quintiles)

Table 3

Pooled Hazard Ratio (HR) and 95% Confidence Interval (CI) of Incident Epithelial Ovarian Cancer, According to Burden of Depression or and Change in Depression Status in the Nurses' Health Study and Nurses' Health Study II

	Cases/person-years	Age-adjusted[a]	Adjusted for ovarian cancer risk factors[b] Hazard ratio (95% CI)	Additionally adjusted for potential mediators[c]
Proportion of follow-up periods with positive depression status[d]				
None	395/1,236,824	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
0<−1/3	47/204,152	0.91 (0.67, 1.24)	0.89 (0.65, 1.21)	0.86 (0.63, 1.18)
1/3<−2/3	52/164,216	1.21 (0.90, 1.62)	1.17 (0.87, 1.56)	1.13 (0.84, 1.51)
>2/3	37/100,561	1.45 (1.03, 2.04)	1.38 (0.98, 1.94)	1.33 (0.94, 1.87)
P_{trend}		0.03	0.06	0.13
Changes in depression status compared to previous assessment[e]				
Persistent negative depression status	442/1,423,045	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Worsening depression status	31/93,594	1.32 (0.91, 1.91)	1.28 (0.88, 1.85)	1.24 (0.85, 1.80)
Improved depression status	18/75,767	0.90 (0.56, 1.45)	0.88 (0.54, 1.41)	0.84 (0.52, 1.35)
Persistent positive depression status	59/164,724	1.42 (1.08, 1.86)	1.34 (1.01, 1.76)	1.29 (0.98, 1.70)

[a] Stratified by age in months, calendar years and cohort

[b] Age-adjusted model plus menopausal status (premenopausal, postmenopausal), parity (nulliparous, 1, 2, 3, >3 children), duration of oral contraceptive use (never, <1, 1 to 5, >5 years), duration of postmenopausal hormone use by type (never, <5, 5 to 10, >10 years for estrogen only and estrogen plus progestin, separately), history of tubal ligation (yes, no), history of hysterectomy (yes, no), and family history of breast cancer or ovarian cancer (yes, no)

[c] Ovarian cancer risk factor model plus body mass index (<20, 20 to <25, 25 to <30, ≥30 kg/m^2), physical activity (<3, 3 to <9, 9 to <18, 18 to <27, ≥27 MET-h/week), smoking (never, past, current), caffeine intake (mg/d, in quintiles) and lactose intake (g/d, in quintiles)

[d] The number of cases was smaller because the analysis was restricted to women returning questionnaires for at least 3 cycles during the follow-up

[e] The number of cases was smaller because the follow-up started from 1996 in NHS and 1997 in NHSII to allow assessment of changes