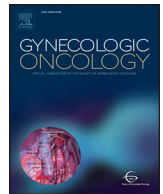




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Depression and risk of epithelial ovarian cancer: Results from two large prospective cohort studies[☆]

Tianyi Huang^{a,b,*}, Elizabeth M. Poole^a, Olivia I. Okereke^{a,b,c}, Laura D. Kubzansky^d, A. Heather Eliassen^{a,b}, Anil K. Sood^e, Molin Wang^{a,b,f}, Shelley S. Tworoger^{a,b}

^a Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

^b Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, United States

^c Department of Psychiatry, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

^d Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, United States

^e Department of Gynecologic Oncology, MD Anderson Cancer Center, Houston, TX, United States

^f Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, United States

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.

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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. Multivariable-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% CI 1.05–1.60). 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 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.

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1. 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

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* Corresponding author at: 181 Longwood Ave., 4th Fl., Boston, MA 02115, United States.

E-mail address: tih541@mail.harvard.edu (T. Huang).

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.

2. Materials and methods

2.1. 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 covariates on biennial 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.

2.2. 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, and 2000 in NHS and in 1993, 1997, and 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 the 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 the past two years was used to indicate current physician-diagnosed depression status.

2.3. 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].

2.4. 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: 5250; NHSII: 244), or had bilateral oophorectomy (NHS: 22,318; NHSII: 5208), menopause due to pelvic irradiation (NHS: 417; NHSII: 92), or diagnosis of cancer other than non-melanoma skin cancer (NHS: 6343; NHSII: 1152) before their first report of depression-related measures or had no assessment on depression (NHS: 9921; 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]. Secondly, 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 examined 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 by behavioral changes following depression, we further

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