Published in final edited form as:

Cancer Causes Control. 2016 May ; 27(5): 661–668. doi:10.1007/s10552-016-0739-0.

A PROSPECTIVE STUDY OF PHOBIC ANXIETY, RISK OF OVARIAN CANCER, AND SURVIVAL AMONG PATIENTS

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Abstract

Purpose—In ovarian cancer patients and mouse models, psychosocial stress is associated with higher circulating markers of angiogenesis and cell migration, impaired immune response, and increasing tumor burden and aggressiveness. In the Nurses' Health Studies (NHS/NHSII), we assessed whether phobic anxiety, a marker of chronic distress, was associated with risk of incident ovarian cancer as well as survival among ovarian cancer patients.

Methods—We used Cox proportional hazards regression to model the relative risks (RR) and 95% confidence intervals (CI) of ovarian cancer incidence and survival by categories of the Crown-Crisp phobic anxiety index (CCI).

Results—We identified 779 cases of ovarian cancer during 2,497,892 person-years of follow-up. For baseline CCI (NHS: 1988; NHSII: 1993), we observed a statistically non-significant increased risk of epithelial ovarian cancer (RR for CCI 4 vs. 0 or 1: 1.14; 95% CI: 0.96–1.36). However, when we updated CCI (NHS: 2004; NHSII: 2005), the associations were attenuated. Pre-diagnosis CCI was not associated with ovarian cancer survival (RR: for 4 vs. 0 or 1: 1.00; 95% CI: 0.77–1.31); results were similar for post-diagnosis CCI.

Conclusions—Distress, as measured by phobic anxiety symptoms, was not associated with ovarian cancer risk, although we cannot rule out a modest association. Future research should explore the role of phobic anxiety and other forms of psychological distress and ovarian cancer risk and survival.

Keywords

anxiety; distress; ovarian cancer; cancer; oncology

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Compliance with ethical standards: This analysis was approved by the institutional review board of Brigham and Women's Hospital. Study participants provided informed consent.

The authors have no conflicts of interest to disclose.

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer death for women in the U.S. and the seventh most fatal worldwide [1, 2]. Although several risk factors are known (e.g., nulliparity, lack of oral contraceptive use), few are easily modifiable. Thus, identifying modifiable risk factors for ovarian cancer is critical for reducing incidence and mortality.

Stress is hypothesized to contribute to cancer etiology [3], but studies linking stress to specific cancers have produced equivocal results. A recent meta-analysis reported a 6% increased risk for cancer associated with chronic stress, but this study did not evaluate ovarian cancer separately [3]. Mouse models suggest that chronic distress leads to larger and more aggressive ovarian tumors [4]; in ovarian cancer patients, chronic distress has been associated with higher levels of circulating markers of inflammation, angiogenesis, and immune activation [5–9]. Taken together, these data suggest that chronic distress, a potentially modifiable exposure, may increase risk of developing ovarian cancer. Further, chronic distress is common: according to the National Comorbidity Survey Replication, the lifetime prevalence of anxiety disorders is 28.8% and the lifetime prevalence of mood disorders is 20.8% [10].

Phobic anxiety, as assessed by the Crown-Crisp phobic anxiety index (CCI), a standardized, validated instrument [11], provides one marker of chronic distress. The CCI addresses common fears and tendencies of avoidance, primarily those reflected in the modern categorizations of panic and phobic disorders [10, 12]. Previous research has demonstrated that the CCI discriminates between individuals with diagnosable anxiety disorders and healthy individuals [11] and is correlated reasonably with other measures from the Middlesex Hospital Questionnaire (free-floating anxiety $\rho = 0.48$, obsessional $\rho = 0.45$, somatic $\rho = 0.42$, depressive $\rho = 0.27$) [11]. This form of anxiety previously has been associated with increased risk of cardiovascular disease and Parkinson's disease, as well as higher levels of inflammatory markers and shorter telomere lengths, in the Nurses' Health Study (NHS) [13–16]. Moreover, because of the generally younger-age at onset and chronic nature of phobic anxiety, the CCI likely reflects long-term exposure to chronic distress [10, 12]. Furthermore, phobic anxiety is among the more chronic and persistent forms of anxiety [17]. Therefore, given its reliability, overlap with other forms of distress, chronicity, and prevalence, we evaluated whether phobic anxiety was associated with increased risk of ovarian cancer in the NHS and NHSII cohorts.

MATERIALS AND METHODS

The Nurses' Health Study (NHS) was established in 1976 among 121,701 US female registered nurses, ages 30 to 55 years; the NHSII was established in 1989 among 116,430 female registered nurses, ages 25 to 42 years. All women completed an initial questionnaire about their lifestyle factors, health behaviors, and medical history, and, since baseline, have been followed biennially by questionnaire to update exposure status and disease diagnoses [18, 19].

ASCERTAINMENT OF PHOBIC ANXIETY

Symptoms of phobic anxiety were self-reported in the NHS (1988 and 2004) and NHSII (1993 and 2005) using the Crown-Crisp phobic anxiety index (CCI) [11]. The CCI is comprised of eight questions (Online Resource 1). Each has two or three possible answers. The responses are summed to derive a total score that ranges from 0 to 16; higher scores indicate higher anxiety. The CCI is fairly reliable in the NHS: Cronbach's alpha for 1988 was 0.62 and the intraclass correlation in women who answered the CCI in 1988 and 2004 was 0.61, indicating that the results are moderately stable over time [15]. Results were similar in NHSII: Cronbach's alpha was 0.58 for 1993 and the ICC comparing women who completed the CCI in both 1993 and 2005 was 0.61. The CCI was assessed in two ways in this analysis: continuously (per 1 standard deviation [SD] change) and grouped into 4 categories (0/1, 2, 3, 4+), as in [13–16]. As a secondary analysis, we analyzed the CCI in 6 categories (0/1, 2, 3, 4/5, 6+).

In the NHS, of the 103,614 participants who responded to the 1988 questionnaire, 84,791 completed the CCI. Of those who did not complete the CCI, the majority (89.8%) received a shortened questionnaire without the CCI. Follow-up through June 2010 was 94.0% of the potential person-years. In the NHSII, of the 107,721 women who responded to the 1993 questionnaire, 86,971 completed the CCI; of those who did not answer the questions, 63.7% received a shortened questionnaire without the CCI. Follow-up through June 2011 was 95.4% of the potential person-years.

DOCUMENTATION OF OVARIAN CANCER CASES AND DEATHS

We collected information about ovarian cancer diagnoses on each questionnaire. Deaths were reported by family members or the US Postal Service; we also checked the National Death Index for deaths. For all reported cases and deaths due to ovarian cancer, we obtained pathology reports pertaining to the ovarian cancer diagnosis. A gynecologic pathologist reviewed the pathology reports to confirm the diagnosis and abstract stage, histology, and invasiveness. In a subset of 215 ovarian cancer cases, concordance between the medical records and the pathologist's review was 98% for invasiveness and 83% for histologic type [20].

STATISTICAL ANALYSIS

The eligible population for this analysis included the 84,791 NHS participants and the 86,971 NHSII participants who completed the 1988 and 1993 CCI questionnaires, respectively. Women diagnosed with cancer (except non-melanoma skin cancer) prior to the baseline year (NHS=6462; NHSII=1605), a bilateral oophorectomy (NHS=11 843; NHSII=2977), menopause due to pelvic irradiation (NHS=54; NHSII=28), or who were missing date of birth (NHS=36; NHSII=187) were excluded. After exclusions, 66,396 NHS participants and 82,174 NHSII participants remained in the analyses. Participants accrued person-time from the time of the return of the 1988/1993 questionnaire until the date of ovarian cancer diagnosis, diagnosis of another cancer (except non-melanoma skin cancer),

bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (NHS: June 1, 2010; NHSII: June 1, 2011).

We used Cox proportional hazards regression to estimate relative risk (RRs) and 95% confidence intervals (CIs) of ovarian cancer for each CCI category compared to those with little to no phobic anxiety (CCI score of 0 or 1). Time since questionnaire return was used as the time scale and two models were used to adjust for potential confounders or mediators. In our primary model, we adjusted for known and suspected ovarian cancer risk factors: duration of oral contraceptive (OC) use, number of children, tubal ligation, family history of ovarian cancer, and menopausal status. In a secondary model, to evaluate whether any observed associations were due to behavioral and lifestyle correlates of stress which may be on the pathway between stress exposure and cancer, we additionally adjusted for body mass index (BMI), smoking, alcohol intake, caffeine intake, total caloric intake, physical activity, and census tract income. We also evaluated post-menopausal hormone therapy (HT) use, beta blocker use, antidepressant medication use, anti-anxiety medication use, and depression as potential mediators; these variables did not change the relative risk estimates and were not included in our final models. All models were stratified on age and calendar time. All adjustment variables were updated whenever updated information was available (usually every 2–4 years).

We additionally performed an analysis evaluating whether pre-diagnosis or post-diagnosis CCI was associated with ovarian cancer survival, adjusting as in the incidence analyses, but additionally adjusting for disease stage and histology. These analyses were limited to invasive ovarian cancer cases. For pre-diagnosis CCI, the time scale was time between diagnosis and death or end of follow-up, whichever occurred first. For post-diagnosis CCI, we used left truncation to account for the delay between diagnosis and completion of the CCI questionnaire. Covariates for the pre-diagnosis CCI analysis were taken from the last questionnaire that was completed prior to ovarian cancer diagnosis; for the post-diagnosis CCI analyses, covariates were taken from the first questionnaire completed after diagnosis.

The NHS and NHSII datasets were pooled using a strata term for cohort in Cox proportional hazards models; we evaluated potential differences between the cohorts using p-heterogeneity from meta-analysis. Main analyses considered both baseline and updated (in 2004/2005) CCI with risk of total ovarian cancer (borderline and invasive). In secondary analyses, we assessed whether results differed by known ovarian cancer risk factors menopausal status, HT use, OC use, family history of ovarian cancer, or current beta blocker use via stratified analysis. To test for interaction, we included multiplicative interaction terms and tested their significance using a likelihood ratio test. As a sensitivity analysis, we examined associations only among women who completed the CCI twice (i.e, baseline – 1988/1993 and updated – 2004/2005). We also assessed the association with change in CCI between the two questionnaires and risk of ovarian cancer. P-values <0.05 were considered statistically significant; all analyses were conducted in SAS v.9.3 (Cary, NC). This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

RESULTS

Women with higher phobic anxiety (CCI score ≥ 4) were similar to those with low anxiety (CCI score 0 or 1) in terms of age, parity, BMI, tubal ligation, family history of ovarian cancer, and menopausal status. Women with higher anxiety were more likely to be current smokers (Table 1).

In our primary models, higher CCI scores at baseline (NHS: 1988; NHSII: 1993) were associated with a suggestive increased risk of ovarian cancer: for a 1 SD change in CCI (2.31 points), the relative risk was 1.05 (95% CI: 0.98–1.13). Similar results were observed when comparing women with CCI ≥ 4 to women with CCI of 0 or 1 (RR: 1.14; 95% CI: 0.96–1.36; Table 2) and when using 6+ as the upper category (Online Resource 2). When we updated the CCI in 2004 (NHS) / 2005 (NHSII), associations were attenuated (CCI ≥ 4 vs 0/1, RR: 1.08 (95% CI: 0.91–1.29)). Additional adjustments for potential behavioral or environmental correlates of phobic anxiety did not substantially change the results (Table 2). To address potential reverse causality, we performed analyses removing the first two and four years of follow-up after the assessment of the CCI; results were not materially changed (data not shown).

In stratified analyses by ovarian cancer risk factors, we observed a stronger association for postmenopausal women using both baseline (P -interaction=0.045; Online Resource 3) and updated (P -interaction=0.024; Online Resource 4) CCI scores. We observed no other statistically significant interactions; however power was limited for these analyses.

Among women who completed both the baseline and follow-up questionnaires, the association with high levels of phobic anxiety was slightly stronger (Online Resource 5), but there was no association between change in CCI score and ovarian cancer risk (Online Resource 6).

There was no association between pre-diagnosis CCI score and survival after diagnosis of invasive ovarian cancer (Table 3); women with a pre-diagnosis CCI ≥ 4 had no difference in risk of dying compared to those with a CCI of 0 or 1 (RR: 1.00; 95% CI: 0.77–1.31). In analyses of post-diagnosis CCI and ovarian cancer survival, results were similar: women with a post-diagnosis CCI ≥ 4 had a non-significant 14% increased risk of dying due to ovarian cancer compared to women with a score of 0 or 1 (RR: 1.14; 95% CI: 0.34–3.82; Table 3). However, there were only 358 ovarian cancer patients who completed the CCI after their diagnosis.

DISCUSSION

In this study, we observed a suggested increased risk of ovarian cancer among women with high levels of phobic anxiety, but no association between phobic anxiety and ovarian cancer-specific survival. Although extensively studied [3, 21–31], the role of stress in cancer incidence and survival remains unclear. In a recent meta-analysis, chronic stress was associated with a 6% increased risk of cancer and a 3% increased risk of death [3]; the associations were stronger for studies with longer follow-up, suggesting that chronic stress may have a greater impact on health than short term stress. However, neither ovarian cancer

nor anxiety was evaluated separately in this meta-analysis; thus, the role of chronic stress in general, and phobic anxiety specifically in ovarian carcinogenesis remain unclear.

There is evidence from basic and clinical studies that stress may promote ovarian carcinogenesis. Mice subjected to physical restraint or social isolation and injected with ovarian cancer cells developed larger and more invasive tumors compared to control mice [4]. Stressed mice had a 2.5-fold increase in tumor weight and nodule count versus controls; 50% of stressed mice had metastases in the liver or spleen compared to none in control mice. Further, distressed animals had higher *VEGF*, *MMP-2*, and *MMP-9* expression, leading to increased angiogenesis and metastasis. Although only modestly associated with ovarian cancer risk in the present study, the CCI has previously been associated with shorter telomeres [15], and with higher circulating levels of inflammatory cytokines among women with diabetes [16], both of which have been related to ovarian cancer risk or progression [32–36].

The associations between baseline CCI were stronger than when we updated the CCI using the follow-up questionnaire; this would seem to contradict the meta-analysis findings that studies with longer follow-up were more likely to observe associations between stress and cancer risk. However, women who did not complete the follow-up questionnaire had, on average, higher baseline CCI scores (mean=3.08) compared to women who completed both questionnaires (mean=2.76). Since the CCI has been associated with risk of sudden cardiac death and fatal coronary heart disease in the NHS [13], it is possible that the attenuation was due to competing risks by these causes of death. However, given the limited sample size for this study (N=779 ovarian cancer cases), it is possible that the suggestive association we observed with baseline CCI is due to chance.

Since experimental studies reported that stressful conditions and induced distress are associated with increased metastases, we assessed the relationship between phobic anxiety and survival after ovarian cancer, observing no association. A limitation of this analysis is that we do not have data on surgery and treatment in the NHS; this may be particularly problematic for our analysis of post-diagnosis CCI and ovarian cancer outcomes, since women who suffer from phobic anxiety may be less likely to complete treatment than those who don't. Pre-diagnosis phobic anxiety was highly correlated with post-diagnosis phobic anxiety among ovarian cancer cases who were diagnosed between the two assessments (Online Resource 7). Although the numbers are small, most women had the same score or changed by 1 or 2 points. No prior study has assessed the association of chronic distress and ovarian cancer; however, in ovarian cancer patients, anxiety, depression, and lack of social support, which may attenuate cancer-related distress, have been associated with elevated levels of circulating IL-6, VEGF, norepinephrine, and MMP-9 [5–9].

Our study has several strengths. First, phobic anxiety was assessed using a validated measure years prior to diagnosis, reducing the likelihood of recall bias. Any measurement error that occurred is likely non-differential with respect to ovarian cancer incidence; therefore our results are likely to be an underestimate of any true association. Further, the CCI is stable over time (Online Resource 8), suggesting that a one-time assessment reflects long-term exposure to anxiety symptoms and that measurement error is low. However,

assessment of phobic anxiety only captures one facet of psychosocial stress and may not fully characterize an individual's subjective experience of stress. For example, coping mechanisms may be important factors in the relationship between chronic distress and cancer risk; we had limited information on coping. However, when we adjusted for available correlates of coping, such as diet, BMI, and physical activity, the associations were not dramatically altered, suggesting that these factors are not important mediators in our analysis. Nevertheless, future studies should consider additional coping variables.

In conclusion, this study suggests that phobic anxiety may be related to a modestly increased risk of ovarian cancer. The role of anxiety in ovarian cancer should be addressed in additional studies. Further, other facets of the psychosocial stress experience, such as depression, should be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the participants and staff of the NHS and NHSII for their valuable contributions as well as the following 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.

Sources of funding: This study was funded through grants from the US National Institutes of Health: UM1 CA186107, UM1 CA176726, and R01 CA163451 and from the US Department of Defense: W81XWH-13-1-0493.

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Table 1
Age-standardized characteristics of NHS and NHSII participants at baseline (NHS: 1988; NHSII: 1993)

	NHS					NHSII				
	Crown-Crisp Phobic Anxiety index ^a					Crown-Crisp Phobic Anxiety index ^a				
	0/1 (n=20 404)	2 (n=11 980)	3 (n=10 137)	4+ (n=23 875)		0/1 (n=31 845)	2 (n=15 791)	3 (n=11 784)	4+ (n=22 754)	
Means (SDs)										
Age (years) ^b	54.4 (7.2)	54.2 (7.2)	54.3 (7.2)	54.5 (7.2)		38.4 (4.6)	38.4 (4.6)	38.4 (4.6)	38.6 (4.6)	
Duration of OC use (years)	2.2 (3.6)	2.1 (3.5)	2.0 (3.4)	1.9 (3.3)		4.2 (4.2)	4.1 (4.1)	4.1 (4.1)	3.9 (4.1)	
Number of children ^c	3.0 (1.7)	3.0 (1.6)	3.0 (1.6)	3.0 (1.6)		1.6 (1.2)	1.7 (1.2)	1.7 (1.2)	1.7 (1.2)	
BMI (kg/m ²)	25.2 (4.6)	25.2 (4.6)	25.5 (4.7)	25.8 (5.0)		24.8 (5.3)	25.1 (5.6)	25.3 (5.7)	25.8 (6.1)	
Alcohol intake (gm/day)	5.2 (10.1)	5.2 (10.0)	4.9 (9.9)	4.9 (10.6)		3.0 (5.7)	3.0 (5.7)	3.1 (6.3)	2.8 (6.0)	
Caffeine intake (gm/day)	234 (234)	236 (236)	230 (233)	226 (238)		222 (202)	228 (203)	231 (204)	239 (213)	
Census tract income (thousands of dollars)	66.7 (27.0)	65.7 (25.9)	64.7 (25.7)	63.3 (24.6)		64.0 (23.5)	63.0 (22.8)	62.5 (22.7)	61.0 (22.0)	
Percentages										
Ever parous	94	94	95	95		75	77	78	79	
Tubal ligation	17	18	18	17		20	20	21	22	
Family history of ovarian cancer ^d	3	3	2	3		1	2	2	2	
Post-menopausal	57	57	57	57		1	1	1	1	
Smoking status										
Never smoker	48	43	43	42		69	66	65	63	
Former smoker	35	38	38	37		22	24	24	24	
Current smoker	17	19	19	21		9	11	11	13	

Values are standardized to the age distribution of the study population.

^aThe Crown-Crisp phobic anxiety index ranges from 0 to 16, with higher scores indicating more anxiety.

^bValue is not age-standardized

^cAmong parous women

^dQueried in 1992 in NHS

Table 2

Associations between Crown-Crisp phobic anxiety index and risk of epithelial ovarian cancer.

NHS	Baseline (NHS: 1988; NHSII: 1993)						Updated (NHS: 2004; NHSII: 2005)					
	Age-adjusted			Multivariate adjusted ¹			Age-adjusted			Multivariate adjusted ¹		
	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Crown-Crisp Anxiety score												
Continuous ³		1.07 (0.99–1.16)	1.06 (0.98–1.15)	1.07 (0.99–1.16)	1.07 (0.99–1.16)	1.07 (0.99–1.16)		1.05 (0.97–1.13)	1.04 (0.96–1.13)	1.05 (0.97–1.13)	1.05 (0.97–1.13)	1.05 (0.97–1.13)
4-level categorization												
0/1	176/360 367	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	182/366 629	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2	102/210 502	1.01 (0.79–1.29)	1.01 (0.79–1.29)	1.01 (0.79–1.29)	1.01 (0.79–1.29)	1.01 (0.79–1.29)	97/209 710	0.96 (0.75–1.23)	0.95 (0.74–1.22)	0.95 (0.74–1.22)	0.95 (0.74–1.22)	0.95 (0.74–1.22)
3	78/176 605	0.91 (0.70–1.19)	0.91 (0.70–1.19)	0.92 (0.70–1.20)	0.92 (0.70–1.20)	0.92 (0.70–1.20)	88/175 262	1.03 (0.79–1.32)	1.02 (0.79–1.32)	1.03 (0.79–1.32)	1.03 (0.79–1.32)	1.03 (0.79–1.32)
4+	235/413 996	1.17 (0.96–1.42)	1.16 (0.95–1.41)	1.17 (0.96–1.42)	1.17 (0.96–1.42)	1.17 (0.96–1.42)	224/409 869	1.11 (0.91–1.35)	1.10 (0.90–1.34)	1.11 (0.91–1.36)	1.11 (0.91–1.36)	1.11 (0.91–1.36)
P-trend		0.15	0.18	0.15	0.15	0.15		0.24	0.28	0.24	0.24	0.24
NHSII	Age-adjusted			Multivariate adjusted ¹			Age-adjusted			Multivariate adjusted ¹		
	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
	Crown-Crisp Anxiety score											
Continuous ³		1.02 (0.88–1.18)	1.03 (0.89–1.19)	1.02 (0.89–1.18)	1.02 (0.89–1.18)	1.02 (0.89–1.18)		1.01 (0.87–1.16)	1.02 (0.88–1.17)	1.01 (0.87–1.16)	1.01 (0.87–1.16)	1.01 (0.87–1.16)
4-level categorization												
0/1	67/522 232	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	70/530 092	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2	39/257 316	1.21 (0.81–1.80)	1.23 (0.83–1.82)	1.22 (0.82–1.82)	1.22 (0.82–1.82)	1.22 (0.82–1.82)	39/255 124	1.20 (0.81–1.77)	1.21 (0.81–1.78)	1.20 (0.81–1.78)	1.20 (0.81–1.78)	1.20 (0.81–1.78)
3	32/190 890	1.30 (0.85–1.98)	1.33 (0.87–2.04)	1.33 (0.87–2.03)	1.33 (0.87–2.03)	1.33 (0.87–2.03)	31/187 867	1.25 (0.82–1.91)	1.28 (0.83–1.95)	1.27 (0.83–1.94)	1.27 (0.83–1.94)	1.27 (0.83–1.94)
4+	50/365 984	1.05 (0.73–1.52)	1.08 (0.75–1.56)	1.06 (0.73–1.54)	1.06 (0.73–1.54)	1.06 (0.73–1.54)	48/363 339	1.00 (0.69–1.44)	1.02 (0.70–1.47)	0.99 (0.69–1.44)	0.99 (0.69–1.44)	0.99 (0.69–1.44)
P-trend		0.66	0.56	0.63	0.63	0.63		0.89	0.80	0.80	0.90	0.90
Combined ⁴	Age-adjusted			Multivariate adjusted ¹			Age-adjusted			Multivariate adjusted ²		
	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	Cases/Person-years	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
	Crown-Crisp Anxiety score											
Continuous ³		1.06 (0.99–1.13)	1.05 (0.98–1.13)	1.05 (0.98–1.13)	1.05 (0.98–1.13)	1.05 (0.98–1.13)		1.04 (0.97–1.11)	1.03 (0.96–1.11)	1.04 (0.97–1.11)	1.04 (0.97–1.11)	1.04 (0.97–1.11)
4-level categorization												
0/1	243/882 599	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	252/896 720	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

NHS	Baseline (NHS: 1988; NHSII: 1993)						Updated (NHS: 2004; NHSII: 2005)					
	Crown-Crisp Anxiety score	Cases/Person-years	Age-adjusted		Multivariate adjusted ¹		Cases/Person-years	Age-adjusted		Multivariate adjusted ¹		Multivariate adjusted ²
			RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	
2		141/467 818	1.06 (0.86–1.31)	1.06 (0.86–1.31)	1.06 (0.86–1.31)	1.06 (0.86–1.31)	136/464 834	1.02 (0.82–1.25)	1.01 (0.82–1.25)	1.01 (0.82–1.25)	1.01 (0.82–1.25)	
3		110/367 496	1.00 (0.80–1.26)	1.00 (0.80–1.26)	1.01 (0.80–1.26)	1.01 (0.80–1.26)	119/363 130	1.08 (0.87–1.34)	1.08 (0.86–1.34)	1.08 (0.87–1.34)	1.08 (0.87–1.34)	
4+		285/779 980	1.15 (0.97–1.37)	1.14 (0.96–1.36)	1.15 (0.96–1.36)	1.15 (0.96–1.36)	272/773 208	1.09 (0.92–1.30)	1.08 (0.91–1.29)	1.09 (0.91–1.30)	1.09 (0.91–1.30)	
P-trend			0.14	0.16	0.15	0.15		0.28	0.32	0.30	0.30	

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¹ Stratified on age in 5-months, calendar time, and study (NHS vs. NHSII); adjusted for duration of OC use, number of children, tubal ligation, family history of ovarian cancer, and menopause status

² Adjusted as in ¹, additionally adjusted for BMI, smoking status (and amount per day among current smokers), alcohol intake, caffeine intake, total caloric intake, physical activity and census tract income.

³ Per 1 SD increase in NHS: 2.38; NHSII: 2.22; combined: 2.31 units

⁴ All *P*-heterogeneity between cohorts > 0.14

Table 3

Association between pre- and post-diagnosis phobic anxiety and ovarian cancer-specific survival.¹

Crown-Crisp Anxiety score	Deaths/Person-years	RR (95% CI) ²	RR (95% CI) ³	RR (95% CI) ⁴	RR (95% CI) ⁵
Pre-diagnosis CCI					
Continuous, per 1 SD increase		0.99 (0.89–1.09)	1.02 (0.92–1.13)	1.01 (0.91–1.12)	0.99 (0.88–1.10)
4-level categorization					
0/1	142/1367	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2	76/722	0.92 (0.67–1.26)	0.79 (0.57–1.09)	0.78 (0.56–1.08)	0.76 (0.55–1.07)
3	63/558	1.11 (0.80–1.55)	1.05 (0.74–1.49)	1.01 (0.71–1.45)	1.00 (0.69–1.45)
4+	149/1561	0.96 (0.75–1.23)	1.03 (0.79–1.34)	1.00 (0.77–1.31)	0.96 (0.72–1.27)
Post-diagnosis CCI					
Continuous, per 1 SD increase		0.93 (0.62–1.38)	0.94 (0.59–1.49)	0.91 (0.54–1.53)	0.87 (0.39–1.95)
4-level categorization					
0/1	37/815	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
2	23/495	1.22 (0.42–3.54)	0.9 (0.25–3.24)	1.31 (0.30–5.70)	10.63 (0.57–197.48)
3	15/353	0.84 (0.26–2.76)	0.82 (0.20–3.41)	0.87 (0.19–3.96)	0.05 (0.00–2.28)
4+	52/929	0.94 (0.40–2.19)	0.99 (0.34–2.86)	1.14 (0.34–3.82)	1.87 (0.25–14.27)

¹ Invasive ovarian cancer only

² Stratified by age, calendar time, and cohort

³ Stratified as in ², adjusted for disease stage and histology

⁴ Stratified/adjusted as in ³, additionally adjusted for duration of OC use, number of children, tubal ligation, family history of ovarian cancer, and menopause status

⁵ Stratified/adjusted as in ⁴, additionally adjusted for BMI, smoking status (and amount per day among current smokers), alcohol intake, caffeine intake, physical activity, and census tract income.