

Posttraumatic Stress Disorder Is Associated with Increased Risk of Ovarian Cancer: A Prospective and Retrospective Longitudinal Cohort Study



Andrea L. Roberts¹, Tianyi Huang^{1,2}, Karestan C. Koenen¹, Yongjoo Kim¹,
Laura D. Kubzansky¹, and Shelley S. Tworoger^{1,3}

Abstract

Ovarian cancer is the deadliest gynecologic cancer. Chronic stress accelerates tumor growth in animal models of ovarian cancer. We therefore postulated that posttraumatic stress disorder (PTSD) may be associated with increased risk of ovarian cancer. We used data from the Nurses' Health Study II, a longitudinal cohort study with 26 years of follow-up, conducted from 1989 to 2015 with 54,710 subjects. Lifetime PTSD symptoms were measured in 2008. Self-reported ovarian cancer was validated with medical records. Risk of ovarian cancer was estimated with Cox proportional hazards models and further adjusted for known ovarian cancer risk factors (e.g., hormonal factors) and health risk factors (e.g., smoking). Fully prospective secondary analyses examined incident ovarian cancer occurring after PTSD assessment in 2008. In addition, we examined associations by menopausal status. During follow-up, 110 ovarian cancers were identified. Women with high PTSD symptoms had 2-fold greater risk of ovarian cancer

versus women with no trauma exposure [age-adjusted HR = 2.10; 95% confidence interval (CI), 1.12–3.95]. Adjustment for health and ovarian cancer risk factors moderately attenuated this association (HR = 1.86; 95% CI, 0.98–3.51). Associations were similar or moderately stronger in fully prospective analyses (age-adjusted HR = 2.38; 95% CI, 0.98–5.76, *N* cases = 50) and in premenopausal women (HR = 3.42; 95% CI, 1.08–10.85). In conclusion, we show that PTSD symptoms are associated with increased risk of ovarian cancer. Better understanding of the underlying molecular mechanisms could lead to interventions that reduce ovarian cancer risk in women with PTSD and other stress-related mental disorders.

Significance: PTSD is associated with ovarian cancer risk, particularly in premenopausal women. Understanding the underlying molecular mechanisms will aid in formulating ways to reduce ovarian cancer risk associated with chronic stress.

Introduction

Ovarian cancer is the most deadly gynecologic cancer (1). Most ovarian cancer risk and protective factors are not easily modifiable at the population level, leading the National Academy of Medicine to recommend in 2016 that identification of novel risk factors be a research priority, with the ultimate goal of improving risk assessment (2). Stress, particularly through the activation of the sympathetic nervous system, has been identified in animal models of ovarian cancer as an accelerant of tumor growth. Patient-derived ovarian cancer xenograft animals that were subjected to chronic stressors (e.g., restraint and social isolation)

developed larger and more invasive tumors than animals not exposed to stressors (3). In experiments with ovarian epithelial and cancer cells, application of stress hormones altered gene expression (4), induced inflammation (5), and triggered production of VEGF and IL8; these alterations have been implicated in tumor angiogenesis and growth (6, 7). In addition, exposure of ovarian cancer cells to stress hormones (e.g., norepinephrine) increases their invasiveness (3, 8, 9). Many of these mechanisms are associated with tumor development, suggesting that stress might increase risk of ovarian cancer.

In epidemiologic studies in humans, several forms of distress, including depression and anxiety, have been related to modestly elevated risk of ovarian cancer (10, 11). Posttraumatic stress disorder (PTSD) is a particularly extreme form of distress occurring in response to trauma (12, 13), and a single study using National Danish medical records found a strong association between treatment for PTSD and subsequent ovarian cancer diagnosis [standardized incident ratio = 2.4; 95% confidence interval (CI), 0.96–4.9], although the estimate was based on only seven PTSD-exposed cases (14).

In this study we examined risk of epithelial ovarian cancer in association with PTSD symptoms in a longitudinal cohort of women. We were able to adjust for known ovarian cancer risk factors (e.g., reproductive and hormonal factors) and health risk factors (e.g., smoking and physical inactivity). As some ovarian cancer risk factors differ by menopausal status (15–18), we additionally stratified by menopausal status. We further

¹Harvard T. H. Chan School of Public Health, Boston, Massachusetts. ²Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts. ³Department of Cancer Epidemiology, Moffitt Cancer Center, Tampa, Florida.

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L.D. Kubzansky and S.S. Tworoger contributed equally to this article.

Corresponding Author: Andrea L. Roberts, Harvard T. H. Chan School of Public Health, 677 Huntington Ave, Boston 02115, MA. Phone: 617-384-8871; Fax: 617-432-8077. E-mail: aroberts@hsph.harvard.edu

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examined associations specifically for type 1 and type 2 cancers, and the serous histotype, the most aggressive form of ovarian cancer.

Patients and Methods

Sample

The Nurses' Health Study II (NHSII) is an ongoing longitudinal study of 116,429 female nurses enrolled in 1989 at ages 24–42 years and followed biennially. In 2008, 60,804 participants who had responded to the most recent biennial questionnaire (2007) were sent a supplemental questionnaire querying lifetime traumatic events and symptoms of PTSD; 54,763 women (90%) responded. This study was approved by the Institutional Review Board of Brigham and Women's Hospital (Boston, MA). Return of questionnaires by mail constituted implied consent. Signed releases were obtained to collect medical records and tissue samples.

Measures

Ovarian cancer. Ovarian cancer diagnosis was self-reported on each biennial questionnaire and validated with medical record review, with follow-up through 2015. We identified additional cases through report by family members and via the National Death Index. We requested pathology reports for all ovarian cancer cases. A gynecologic pathologist blinded to women's exposure status reviewed pathology reports to confirm diagnosis and abstract information on morphology, histotype, stage, and grade. Concordance between a centralized review of slides and pathology report abstraction ranged from 78% for histotype to 94% for morphology (19).

Trauma and PTSD. Lifetime experience of 15 potentially traumatic events (e.g., car accident and assault) and an additional unnamed "other" traumatic event were queried in 2008 with a modified version of the Brief Trauma Interview (eTable in ref. 20). Women were asked to identify the event they considered the most stressful and the year of this worst event. The year of their first traumatic event was also queried. Seven PTSD symptoms related to the worst event were queried with the Brief Screening Scale for DSM-IV PTSD (e.g., "Became jumpy or got easily startled by ordinary noises," see eTable for all events queried; ref. 21). Women were also asked their age the last time they experienced any of the symptoms. In a validation study using gold-standard structured diagnostic interviews for PTSD, a cutoff ≥ 4 of seven PTSD symptoms had sensitivity = 80.3%, specificity = 97.3%, and a cutoff ≥ 6 had sensitivity = 38.0%, specificity = 99.5% (21). For each year of the study, PTSD symptoms and trauma exposure were jointly coded as: no trauma exposure (reference group), trauma and no PTSD symptoms, 1–3 symptoms (subclinical), 4–5 symptoms (moderate), 6–7 PTSD symptoms (high), and trauma, PTSD symptoms unknown. Before their first trauma, or if they did not report any trauma, women were categorized as "no trauma exposure." Following their worst trauma, women were categorized according to their reported PTSD symptoms (e.g., no symptoms, 1–3, 4–5, or 6–7). After their first but before their worst trauma, women were categorized as "trauma, PTSD symptoms unknown." To reduce respondent burden, we queried PTSD symptoms only related to the trauma selected as "worst." Therefore, PTSD symptoms following prior traumas are unknown. If their first and worst trauma were the

same, PTSD symptoms were categorized with respect to that single trauma. A small number of women were missing data on PTSD and were excluded (2.4%, $N = 1,297$; $N = 53,466$ had complete data). Women who reported illness as their worst trauma were excluded, to reduce the possibility that ovarian cancer or related illness was the trauma that triggered PTSD symptoms ($N = 2,516$; N cases = 48).

Time-updated ovarian cancer risk factors. Lifetime oral contraceptive use was queried in 1989 and updated biennially through 2009. Duration of oral contraceptive use was categorized as: never, <1 , >1 –4, or >4 years. Parity, defined as number of pregnancies lasting ≥ 6 months, was queried retrospectively in 1989, updated biennially, and categorized: none, 1, 2, 3, or ≥ 4 . Tubal ligation (ever/never) was queried biennially, 1989–2009. Postmenopausal hormone use was queried biennially, 1989–2013, and categorized as: never, estrogen ever, estrogen plus progesterone ever, or other hormone use ever. History of breast cancer in mother and sisters (any/none) was queried in 1989, 1997, and every subsequent 4 years. History of ovarian cancer in mother and sisters (any/none) was queried in 1993 and every subsequent 4 years.

Time-updated health risk factors. Smoking (current, past, and never) was queried at each biennial questionnaire. Past-year leisure-time physical activity was queried six times with a validated questionnaire (22) and categorized in six levels based on metabolic equivalent hours/week. Body mass index (BMI, kg/m^2) was calculated from self-reported height in 1989 and biennially reported weight. Self-reported weight had good reliability in a validation study (23). In 1989, women reported their weight at age 18 (24) and reported their somatotype (body shape) at age 5 by choosing from a pictogram of nine shapes ranging from extremely thin to morbidly obese. Indicators of depression were assessed regularly across follow-up via self-reported clinician diagnosis, self-reported use of antidepressants, and a five-item depressive symptom questionnaire.

Time-updated variables used for censoring. Removal of ovaries, pelvic radiation, and breast cancer diagnosis were queried at each biennial questionnaire. Deaths of cohort members were identified by family members, the U.S. Postal Service, and the National Death Index.

Analyses

We evaluated prevalence of ovarian cancer and health-risk factors by levels of PTSD symptoms at baseline in 1989. To estimate risk of ovarian cancer in association with trauma and PTSD symptoms across the full follow-up period, we fit Cox proportional hazards models with age in months as the time measure using PROC PHREG (SAS Institute). In primary analyses, categorical trauma/PTSD status 1 year prior to the ovarian cancer risk period was used as the exposure (e.g., PTSD status in 1990 was the exposure for risk of ovarian cancer incidence 1991–1992), to ensure that PTSD preceded disease diagnosis. We conducted a test of trend across levels of PTSD exposure, excluding person-time when PTSD symptoms were unknown. We additionally examined PTSD symptoms as a continuous variable in association with ovarian cancer development. We conducted a secondary fully prospective analysis, examining lifetime trauma/PTSD status at the return of the PTSD questionnaire (2008) as a predictor of

incident ovarian cancer from 2009 to 2015. In all analyses, women were censored at confirmed ovarian cancer (cases), or at the earliest of: self-reported ovarian cancer not confirmed by medical records, bilateral oophorectomy, pelvic radiation, self-reported breast cancer diagnosis, death, or end of follow-up (noncases).

We assessed the impact of adjusting for ovarian cancer risk factors, including history of tubal ligation (25), parity (26), oral contraceptive use (27), postmenopausal hormone use (28), and family history of breast and ovarian cancer (29). Similarly, we investigated health risk factors often altered by PTSD, further adjusting for smoking, BMI, and physical activity (30). We considered adjustment for somatotype at age 5, BMI at age 18, current BMI, and change in BMI from age 18 to current age as predictors of ovarian cancer individually and in combination. The model with change in BMI from age 18 was best fitting by Akaike information criterion therefore we subsequently included only that variable in models. Because many ovarian cancer risk factors have different associations by menopausal status and by tumor histotype (15–18, 31), we examined risk of ovarian cancer in association with PTSD separately for premenopausal and postmenopausal women. In addition, we specifically examined type 1 cancers, type 2 cancers, and cancers with high-grade serous histology, the most common and aggressive form of the disease. We characterized women with other ovarian cancer types as noncases and censored them at the time of their diagnosis.

We conducted several additional analyses. First, as PTSD of longer duration and active versus remitted PTSD symptoms may be associated with increased disease risk (32), we investigated the association of PTSD duration and PTSD symptom remission with ovarian cancer risk. For women who were no longer experiencing symptoms at the time of the PTSD questionnaire, PTSD was considered remitted following the age at which they reported last experiencing symptoms. Second, as depression often cooccurs with PTSD and has been associated with modestly increased risk of ovarian cancer, we examined associations of PTSD with ovarian cancer further adjusted for history of depression. Third, to investigate the possibility that symptoms of undiagnosed ovarian cancer increased risk for PTSD (the reverse of our hypothesis), we calculated the time from worst traumatic event to ovarian

cancer diagnosis and examined the type of trauma that precipitated PTSD symptoms by cancer status.

Fourth, to estimate the likelihood that unmeasured confounders could account for an association between PTSD and ovarian cancer, we calculated the minimum association an unmeasured confounder would need to have with both PTSD and ovarian cancer to fully account for the association of PTSD with ovarian cancer in the fully adjusted model, using the E-value (33).

Fifth, As 1,714 women died before the PTSD data collection in 2008, to examine possible bias from these deaths, we conducted inverse-probability-of-survival-weighted analyses. We calculated probability of surviving until 2008 based on covariates at baseline in 1989, including age, BMI, height, exercise, pack-years of cigarette smoking, alcohol consumption, body shape at age 5, cancer history, occurrence of menopause, ovary removal, use of beta blockers, parity, race, and ethnicity. We then estimated HRs for the age-adjusted model weighted by the inverse of the probability of survival.

Results

At cohort enrollment, women with high (6–7) PTSD symptoms versus women without trauma exposure were more likely to be current smokers (16.5% vs. 9.4%), have had a tubal ligation (17.8% vs. 13.9%), and have used oral contraceptives (86.8% vs. 80.8%; Table 1). The sample was 95% white.

Among 49,443 women followed for up to 26 years, there were 110 incident ovarian cancers across 1,158,732 person-years. Women with high PTSD symptoms versus women without trauma exposure were at greater risk of ovarian cancer, adjusting for age (HR = 2.10; 95% CI, 1.12–3.95; *P* = 0.02; Table 2; Analysis 1a, Model 1). Women with moderate (4–5) PTSD symptoms were also at elevated risk of ovarian cancer, but this did not reach statistical significance (HR = 1.28; 95% CI, 0.69–2.38; *P* = 0.43). Women with trauma and no PTSD symptoms and women with 1–3 symptoms had somewhat lower risk of ovarian cancer compared with women with no trauma exposure, although these differences were not statistically significant (HR_{no symptoms} = 0.65; 95% CI, 0.36–1.18 and HR_{1–3 symptoms} = 0.79; 95% CI, 0.45–1.37). In an age-adjusted model with PTSD symptoms

Table 1. Health-related behaviors and ovarian cancer risk factors by trauma exposure and PTSD symptoms at cohort enrollment, NHSII, 1989 (*N* = 49,443)

		Total	No trauma	Trauma, no PTSD symptoms	1–3 PTSD symptoms	4–5 PTSD symptoms	6–7 PTSD symptoms	Trauma, PTSD symptoms unknown
Age, years	<i>N</i>	49,443	15,378	9,482	9,259	3,827	2,225	9,248
	Mean (SD)	34.6 (4.6)	33.9 (4.8)	35.4 (4.5)	35.1 (4.4)	35.2 (4.4)	35.1 (4.3)	34.2 (4.6)
Race, white	% (<i>N</i>)	95.7 (47,258)	95.6 (9,067)	95.6 (9,067)	95.0 (8,787)	95.3 (3,648)	94.9 (2,112)	96.0 (8,878)
Change in BMI since age 18	Mean (SD)	2.6 (3.7)	2.4 (3.5)	2.7 (3.7)	2.8 (3.6)	3.0 (4.0)	2.9 (4.2)	2.6 (3.7)
Family history of breast or ovarian cancer	% (<i>N</i>)	5.8 (2,858)	5.8 (891)	5.7 (526)	5.7 (527)	7.1 (271)	6.2 (138)	5.4 (498)
Smoking, current	% (<i>N</i>)	11.2 (5,554)	9.4 (1,439)	10.9 (1,037)	12.0 (1,109)	12.3 (470)	16.5 (368)	12.2 (1,131)
Physical activity, <3 metabolic equivalent hours/week	% (<i>N</i>)	14.1 (6,964)	14.4 (2,212)	14.5 (1,380)	14.3 (1,326)	13.0 (499)	15.6 (346)	13.0 (1,199)
Parity, none	% (<i>N</i>)	30.0 (14,810)	35.1 (5,394)	23.2 (2,201)	27.3 (2,523)	27.8 (1,064)	31.4 (699)	31.7 (2,928)
Tubal ligation, ever	% (<i>N</i>)	16.2 (8,003)	13.9 (2,133)	18.3 (1,737)	18.1 (1,674)	16.7 (640)	17.8 (396)	15.3 (1,418)
Oral contraceptive use, never	% (<i>N</i>)	16.5 (8,141)	19.2 (2,954)	16.1 (1,524)	14.6 (1,356)	13.7 (523)	13.2 (293)	15.9 (1,466)
Menopause status, postmenopausal	% (<i>N</i>)	0.4 (203)	0.4 (62)	0.4 (36)	0.5 (43)	0.4 (17)	0.4 (9)	0.4 (34)
Hormone use among postmenopausal women, any	% (<i>N</i>)	63.1 (128)	59.4 (38)	75.0 (27)	51.2 (22)	58.8 (10)	66.7 (6)	73.5 (25)

Table 2. Risk of ovarian cancer by trauma exposure and PTSD symptoms, NHSII, 1989–2015

	Cases/ person-years	Model 1: adjusted for age	Model 2: model 1 further adjusted for ovarian cancer risk factors HR (95% CI)	Model 3: model 2 further adjusted for health risk factors
Analysis 1: full follow-up, 1989–2015 (N = 49,443)				
Analysis 1a: trauma/PTSD in categories				
No trauma	25/284,582	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Trauma, no PTSD	20/288,658	0.65 (0.36–1.18)	0.66 (0.37–1.20)	0.64 (0.35–1.15)
1–3 PTSD symptoms	25/287,873	0.79 (0.45–1.37)	0.78 (0.45–1.36)	0.76 (0.43–1.34)
4–5 PTSD symptoms	17/122,473	1.28 (0.69–2.38)	1.23 (0.66–2.28)	1.18 (0.63–2.21)
6–7 PTSD symptoms	16/70,480	2.10 (1.12–3.95) ^a	1.92 (1.02–3.62) ^b	1.86 (0.98–3.51)
Test of trend ^a		P = 0.02	P = 0.04	P = 0.048
Trauma, PTSD symptoms unknown	7/103,360	1.55 (0.64–3.72)	1.51 (0.63–3.65)	1.45 (0.60–3.49)
Analysis 1b: PTSD as a continuous variable				
PTSD, per symptom	103/1,054,067	1.11 (1.02–1.21) ^b	1.10 (1.01–1.20) ^b	1.10 (1.01–1.20) ^b
Analysis 2: prospective follow-up, 2009–2015 (N = 42,015)				
Analysis 2a: trauma/PTSD in categories				
No trauma	11/48,525	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Trauma, no PTSD	11/66,597	0.73 (0.32–1.69)	0.70 (0.30–1.63)	0.68 (0.29–1.59)
1–3 PTSD symptoms	14/69,280	0.87 (0.39–1.92)	0.82 (0.37–1.82)	0.83 (0.37–1.86)
4–5 PTSD symptoms	5/30,175	0.74 (0.26–2.14)	0.69 (0.24–2.02)	0.70 (0.24–2.04)
6–7 PTSD symptoms	9/17,007	2.38 (0.98–5.76)	2.15 (0.88–5.26)	2.20 (0.89–5.41)
Test of trend		P = 0.16	P = 0.23	P = 0.20
Analysis 2b: PTSD as a continuous variable				
PTSD, per symptom	50/231,584	1.09 (0.94, 1.25)	1.07 (0.94, 1.21)	1.07 (0.94, 1.21)

^aPerson-time when PTSD symptoms were unknown was excluded from the test of trend across trauma/PTSD levels and the analysis of PTSD as a continuous variable. In the prospective analysis, there was no person-time with PTSD symptoms unknown.

^bP < 0.05. Ovarian cancer risk factors include family history of ovarian and breast cancer, tubal ligation, parity, postmenopausal hormone use, and oral contraceptive use. Health risk factors include smoking, change in BMI since age 18, and physical activity.

coded as a continuous variable, each additional symptom was associated with 11% increased risk of cancer (HR = 1.11; 95% CI, 1.02–1.21; P < 0.05; Table 2; Analysis 1b). Further adjustment for ovarian cancer risk factors and health risk factors accounted for some of the PTSD–ovarian cancer association, but it remained statistically significant or nearly significant. Worst traumatic events substantially preceded ovarian cancer diagnoses among women with high PTSD symptoms (median = 32 years; interquartile range = 20–42).

To evaluate more stringently whether PTSD preceded ovarian cancer diagnosis, we considered associations only among women who had not been diagnosed with ovarian cancer at the time of the 2008 PTSD assessment. Fifty women were diagnosed with ovarian cancer from 2009 to 2015, across 231,584 person-years. The association of high PTSD symptoms with risk of ovarian cancer was somewhat stronger in this analysis (HR_{high PTSD symptoms} = 2.38; 95% CI, 0.98–5.76; P = 0.06; Table 2; Analysis 2a; Model 1), although it did not reach statistical significance, likely due to the small number of cases. Associations were slightly attenuated after

adjustment for ovarian cancer risk factors and other health risk factors (Table 2; Analysis 2a; Models 2 and 3). Moderate PTSD symptoms were not associated with ovarian cancer in these analyses.

In additional analyses, the association of PTSD with ovarian cancer incidence was stronger among premenopausal women (N cases = 44; HR_{high PTSD symptoms} = 3.42; 95% CI, 1.08–10.85) than postmenopausal women (N cases = 56; HR_{high PTSD symptoms} = 1.36; 95% CI, 0.58–3.20; P_{interaction} = 0.05; Table 3). Results were similar when restricted to type 1 (N cases = 39; HR_{high PTSD symptoms} = 2.08; 95% CI, 0.75–5.77), type 2 (N cases = 70; HR_{high PTSD symptoms} = 2.12; 95% CI, 0.95–4.75), and high-grade serous cases (N cases = 58; HR_{high PTSD symptoms} = 2.64; 95% CI, 1.09–6.42; Table 4).

Risk of ovarian cancer was somewhat lower among women whose PTSD symptoms had remitted versus women with active symptoms, both compared with the reference, although CIs overlapped (remitted, HR_{high PTSD symptoms} = 1.85; active, HR_{high PTSD symptoms} = 2.66; Table 5), but PTSD duration was not associated

Table 3. Risk of ovarian cancer by trauma exposure and PTSD symptoms by menopausal status, NHSII, 1989–2015

	Premenopausal women (N cases = 44)		Postmenopausal women (N cases = 56)	
	Cases/person-years	HR (95% CI)	Cases/person-years	HR (95% CI)
Trauma and PTSD				
No trauma	7/204,867	1.0 (Reference)	16/62,751	1.0 (Reference)
Trauma, no PTSD	6/184,731	0.82 (0.27–2.46)	13/81,796	0.57 (0.27–1.19)
1–3 PTSD symptoms	10/180,494	1.34 (0.51–3.54)	12/83,393	0.51 (0.24–1.08)
4–5 PTSD symptoms	10/74,526	3.51 (1.33–9.28) ^b	6/37,111	0.56 (0.22–1.44)
6–7 PTSD symptoms	5/42,920	3.42 (1.08–10.85) ^b	8/20,755	1.36 (0.58–3.20)
Test of trend ^a		P = 0.002		P = 0.95
Trauma, PTSD symptoms unknown	6/92,387	2.40 (0.79–7.27)	1/6,513	1.32 (0.16–10.8)

NOTE: Women with uncertain menopausal status were excluded.

^aPerson-time when PTSD symptoms were unknown was excluded from the test of trend.

^bP < 0.05.

Table 4. Risk of type 1, type 2, and high-grade serous ovarian cancer by trauma exposure and PTSD symptoms, NHSII, 1989–2015 (*N* = 49 443, *N* type 1 = 39, *N* type 2 = 70, *N* high-grade serous = 58)

	Type 1 cancers		Type 2 cancers		High-grade serous cancers	
	Adjusted for age		Adjusted for age		Adjusted for age	
	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)	Cases/ person-years	HR (95% CI)
Trauma and PTSD						
No trauma	10/284,582	1.0 (Reference)	15/284,582	1.0 (Reference)	11/284,505	1.0 (Reference)
Trauma, no PTSD	5/288,658	0.42 (0.14–1.22)	15/288,658	0.81 (0.40–1.67)	13/288,619	0.96 (0.43–2.15)
1–3 PTSD symptoms	8/287,873	0.64 (0.25–1.62)	17/287,873	0.90 (0.45–1.80)	13/287,851	0.95 (0.42–2.13)
4–5 PTSD symptoms	7/122,473	1.32 (0.75–3.49)	9/122,473	1.13 (0.49–2.6)	8/122,450	1.39 (0.56–3.48)
6–7 PTSD symptoms	6/70,480	2.08 (0.75–5.77)	10/70,480	2.12 (0.95–4.75)	9/70,480	2.64 (1.09–6.42) ^b
Test of trend ^a		<i>P</i> = 0.10 ^a		<i>P</i> = 0.11 ^a		<i>P</i> = 0.05 ^a
Trauma, PTSD symptoms unknown	3/103,360	1.11 (0.29–4.19)	4/103,360	1.99 (0.62–6.40)	4/103,328	2.38 (0.71–7.93)

NOTE: Type 1 cancers include grade 1 serous, mucinous, endometrioid, clear cell, and grade 1 mixed. Type 2 cancers include grades 2, 3, and unknown grade serous, poorly differentiated, transitional/Brenner, carcinosarcoma, and grades 2 and 3 mixed. In each analysis, women who developed other ovarian cancer types were considered noncases and were censored at the time of their diagnosis.

^aPerson-time when PTSD symptoms were unknown was excluded from the test of trend.

^b*P* < 0.05.

with ovarian cancer risk (per 10 years, HR_{high PTSD symptoms} = 0.93; 95% CI, 0.67–1.28). In analyses restricted to women with depression data, associations of PTSD with ovarian cancer were somewhat stronger in models further adjusted for history of depression (*N* cases = 94, age-adjusted model: HR_{high PTSD symptoms} = 2.23, 95% CI = 1.15–4.32; further adjusted for history of depression: HR_{high PTSD symptoms} = 2.40, 95% CI = 1.21–4.75).

There were no noteworthy differences in age at trauma or trauma type by ovarian cancer development (Table 6). In exploratory analyses, we examined tumor characteristics (e.g., histology and morphology) by trauma/PTSD symptoms and found no differences (Table 7; *P* > 0.05 for all).

In models weighted for the inverse of the probability of surviving until the PTSD data collection in 2008, the association of PTSD with ovarian cancer was similar to that in unweighted models (weighted, HR_{high PTSD symptoms} = 2.11; 95% CI, 1.12–3.98; *P* < 0.05). In E-value analyses, we calculated that an unmeasured confounder, if equally associated with PTSD and ovarian cancer, would have to be associated at HR = 3.15 to fully account for the association of high PTSD symptoms with ovarian cancer in the fully adjusted model (33).

Table 5. Risk of ovarian cancer by trauma exposure and PTSD symptoms, remitted versus active symptoms, NHSII, 1989–2015 (*N* = 49,443)

	All follow-up, 1989–2015	
	Cases/ person-years	Risk of ovarian cancer, adjusted for age HR (95% CI)
Trauma and PTSD		
No trauma	25/284,582	1.0 (Reference)
Trauma, no PTSD	20/288,658	0.65 (0.36–1.18)
1–3 PTSD symptoms	25/287,873	0.79 (0.45–1.37)
4–5 PTSD symptoms, remitted	11/67,067	1.10 (0.54–2.26)
4–5 PTSD symptoms, active	6/55,406	1.78 (0.71–4.46)
6–7 PTSD symptoms, remitted	10/33,963	1.85 (0.88–3.91)
6–7 PTSD symptoms, active	6/36,518	2.66 (1.06–6.67) ^a
Trauma, PTSD symptoms unknown	7/103,360	1.62 (0.67–3.93)

^a*P* < 0.05.

Discussion

In this unique study, with the ability to adjust for individual-level ovarian cancer risk factors and a range of health behaviors, we observed a two-fold higher risk of ovarian cancer among women with high PTSD symptoms compared with women unexposed to traumatic events. Adjusting for ovarian cancer risk factors and health behaviors related to PTSD only modestly attenuated the observed association, leaving open the possibility that hormonal, immune, or other biological changes following PTSD may increase risk of ovarian cancer. The results were similar in sensitivity analyses with follow-up after completion of the PTSD questionnaire, albeit with a smaller number of cases. Importantly, the association remained statistically significant for women diagnosed with the high-grade serous histotype of ovarian cancer, the most common and aggressive form of the disease.

The association of PTSD with ovarian cancer was stronger for premenopausal compared with postmenopausal cases, although these subgroup analyses were based on fewer cases. Some evidence suggests that the reproductive time period, when the ovaries are most active, may be a window of susceptibility to carcinogenic exposures. Many risk factors for ovarian cancer are exposures that specifically occur in the premenopausal period (e.g., oral contraceptive use and tubal ligation), or exhibit stronger associations with ovarian cancer in the premenopausal period (e.g., hysterectomy and physical activity; ref. 34).

Our results are consistent with prior research examining measures of distress and risk of ovarian cancer. Notably, a registry-based study observed a similar standardized incidence ratio (2.4; 95% CI, 0.96–4.9) among women with a PTSD diagnosis versus those without (14). While not statistically significant, these results were highly similar to our findings. Prior studies have also found that depression was associated with modestly increased risk of epithelial ovarian cancer, although not use of antidepressant medications (10, 35, 36). Interestingly, our study showed a suggestion of a linear trend with increasing symptoms and higher ovarian cancer risk. Future studies should consider associations by symptom severity, particularly in women who have no or low PTSD symptoms after a trauma, as this may represent a group with high resilience.

We found some support for our hypothesis that women with active versus remitted PTSD symptoms would have higher risk of ovarian cancer, although CIs were wide. Although few studies

Table 6. Characteristics of worst trauma exposure by PTSD symptoms in women with and without subsequent ovarian cancer, end of follow-up (*N* = 37,777)

	No PTSD symptoms		1-3 PTSD symptoms		4-5 PTSD symptoms		6-7 PTSD symptoms	
	No ovarian cancer	Ovarian cancer	No ovarian cancer	Ovarian cancer	No ovarian cancer	Ovarian cancer	No ovarian cancer	Ovarian cancer
<i>N</i>	12,375	17	14,456	25	6,468	17	3,698	16
Age at worst event, years	Median (IQR) 27 (21-35)	25 (22-32)	28 (18-40)	26 (21-37)	29 (17-42)	29 (18-40)	28 (15-42)	24 (16-39)
Type of worst event								
Interpersonal violence	% (<i>N</i>) 22.0 (2,720)	23.5 (4)	40.0 (5,824)	32.0 (8)	52.2 (3,379)	29.4 (5)	57.6 (2,130)	52.3 (9)
Sudden death of loved one	% (<i>N</i>) 15.4 (1,901)	5.9 (1)	16.1 (2,349)	8.0 (2)	13.7 (887)	23.5 (4)	11.4 (420)	18.7 (3)
Other events	% (<i>N</i>) 62.7 (7,754)	70.6 (12)	39.7 (5,778)	56.0 (14)	30.9 (1,999)	35.3 (6)	27.9 (1,030)	25.0 (4)

NOTE: Table does not include women with no lifetime trauma exposure. Interpersonal violence includes childhood physical abuse, physical attack, unwanted sexual contact, sexual harassment at work, unnamed event (unnamed events have been shown to cluster with interpersonal violence). Other events include serious accident, natural or man-made disaster, miscarriage, death of a child, pregnancy complication, serious injury, witnessing serious injury or death, service in a war zone, and treating civilians with traumatic injuries. The "No PTSD symptoms" group includes women who had not had their worst trauma before being censored, therefore, numbers do not sum to the column total.

have examined the associations of active versus remitted PTSD symptoms on health outcomes, a single study in the same cohort found increased risk of cardiovascular disease in women with active symptoms and no increased risk in women with remitted symptoms (32). It is worth noting that we do not have information on factors driving the remission, regarding whether remission was spontaneous or due to treatment. It is possible that downstream biologic consequences of chronic stress related to PTSD may be more manifest when women are actively experiencing symptoms and thus have a greater health impact.

PTSD is characterized by activation of the sympathetic nervous system and presence of higher concentrations of epinephrine and norepinephrine (37-41). Animal models indicate that the effect of stress on ovarian carcinogenesis is mediated largely through catecholamine binding to the β_2 -adrenergic receptor and activating the downstream signaling pathway (3, 8, 42). Of relevance to carcinogenesis, the sympathetic nervous system regulates local norepinephrine levels via sympathetic neural innervation, including in healthy ovaries and ovarian tumors (43). Norepinephrine binding to β_2 -adrenergic receptor on ovarian tumors activates

inflammation, angiogenesis, and cell motility (7, 44). Interestingly, depression and anxiety were more strongly associated with increased risk of β_2 -adrenergic receptor-positive ovarian cancer tumors than β_2 -adrenergic receptor-negative tumors, supporting this as an important biologic mechanism of action (45). Furthermore, stress activates signaling pathways that reduce apoptosis and enhance tumor growth via increased expression of *DUSP1*, a phosphatase related to chemoresistance and protection from apoptosis in ovarian cancer cell lines (46), and activation of cAMP-PKA signaling pathways (3, 47). Thus, stress may promote ovarian cancer development by inhibiting key defenses against unrestrained cell growth.

Our study has several limitations. As is common in large epidemiologic studies, to reduce cost and respondent burden we relied on self-report of PTSD symptoms and did not conduct diagnostic interviews, although evidence indicates that the symptom screener provides reasonably valid information about PTSD (21). Lifetime trauma exposure and PTSD symptoms were queried retrospectively at a single timepoint. We conducted several sensitivity analyses to consider the potential impact of

Table 7. Characteristics of ovarian cancer in women by trauma exposure and PTSD symptoms (*N* = 110)

		No trauma	Trauma, no PTSD	1-3 PTSD symptoms	4-5 PTSD symptoms	6-7 PTSD symptoms	Trauma, PTSD symptoms unknown
<i>N</i>		25	20	25	17	16	7
Age at cancer diagnosis, years	Mean (SD)	52.6 (8.8)	54.4 (5.2)	53.8 (5.9)	50.3 (6.9)	55.0 (7.7)	42.9 (9.6)
Origin							
Ovarian	% (<i>N</i>)	88.0 (22)	80.0 (16)	80.0 (20)	88.2 (15)	93.8 (15)	100.0 (7)
Fallopian	% (<i>N</i>)	8.0 (2)	10.0 (2)	8.0 (2)	11.8 (2)	6.3 (1)	0 (0)
Peritoneal	% (<i>N</i>)	4.0 (1)	10.0 (2)	12.0 (3)	0 (0)	0 (0)	0 (0)
Histology							
Serous	% (<i>N</i>)	48.0 (12)	70.0 (14)	56.0 (14)	64.7 (11)	62.5 (10)	57.1 (4)
Mucinous	% (<i>N</i>)	12.0 (3)	5.0 (1)	0 (0)	5.9 (1)	12.5 (2)	0 (0)
Endometrioid	% (<i>N</i>)	16.0 (4)	10.0 (2)	4.0 (1)	17.7 (3)	6.3 (1)	28.6 (2)
Clear cell	% (<i>N</i>)	8.0 (2)	5.0 (1)	20.0 (5)	5.9 (1)	6.3 (1)	0 (0)
Brenner	% (<i>N</i>)	4.0 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Mixed	% (<i>N</i>)	4.0 (1)	0 (0)	0 (0)	(1)	(1)	14.3 (1)
Morphology							
Invasive	% (<i>N</i>)	60.0 (15)	50.0 (10)	44.0 (11)	88.2 (15)	62.5 (10)	57.1 (4)
Borderline	% (<i>N</i>)	24.0 (6)	25.0 (5)	20.0 (5)	5.9 (1)	25.0 (4)	42.8 (3)
Stage							
Limited to ovaries	% (<i>N</i>)	44.0 (11)	45.0 (9)	48.0 (12)	29.4 (5)	43.8 (7)	71.4 (5)
Pelvic extension	% (<i>N</i>)	12.0 (3)	15.0 (3)	0 (0)	5.9 (1)	0 (0)	14.3 (1)
Intraperitoneal metastasis	% (<i>N</i>)	32.0 (8)	25.0 (5)	20.0 (5)	64.7 (11)	43.8 (7)	14.3 (1)
Distant metastases	% (<i>N</i>)	0 (0)	0 (0)	8.0 (2)	0 (0)	0 (0)	0 (0)

NOTE: $\chi^2 P > 0.05$ for all. Some percentages do not sum to 100 due to missing data.

survival bias and saw very similar results. We also note that there were only 16 ovarian cancer cases among women exposed to high PTSD symptoms therefore it is important to replicate our findings in a cohort with more cases. Finally, many risk factors differ by histotype, and, with the exception of type 1, type 2, and high-grade serous tumors, we were unable to examine specific histotypes because of the limited number of cases. Our study also has important strengths, including that ovarian cancer diagnoses were confirmed by medical record review, and health-related behaviors and ovarian cancer risk factors were queried repeatedly over a long follow-up. It is unlikely that ovarian cancer preceding PTSD could account for our findings, as results were confirmed in fully prospective analyses, we excluded women who listed illness as their worst traumatic event, and PTSD-triggering traumas occurred on average decades before ovarian cancer diagnosis.

Our data suggest that PTSD symptoms following traumatic events may be associated with increased risk of ovarian cancer decades later. This finding is consistent with animal models and other human studies showing a relationship of depression and anxiety with ovarian cancer development, strongly supporting further exploration of this pathway as an etiologic factor in ovarian cancer development. Replication of these results may suggest future consideration of chronic stress measures in risk assessment tools. In addition, better understanding of biological pathways could lead to interventions to reduce risk of ovarian cancer in women with PTSD and, potentially, other distress-related disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The authors assume full responsibility for analyses and interpretation of these data. The funders had no role in: the design and conduct of the study;

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Authors' Contributions

Conception and design: A.L. Roberts, K.C. Koenen, L.D. Kubzansky, S.S. Tworoger

Development of methodology: A.L. Roberts, K.C. Koenen, L.D. Kubzansky, S.S. Tworoger

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): T. Huang, K.C. Koenen

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.L. Roberts, T. Huang, K.C. Koenen, L.D. Kubzansky, S.S. Tworoger

Writing, review, and/or revision of the manuscript: A.L. Roberts, T. Huang, K.C. Koenen, Y. Kim, L.D. Kubzansky, S.S. Tworoger

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): T. Huang, K.C. Koenen, L.D. Kubzansky

Study supervision: K.C. Koenen, L.D. Kubzansky

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