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Posttraumatic Stress Disorder and Cancer Risk: A Nationwide Cohort Study

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Abstract

Background—The association between stress and cancer incidence has been studied for more than seven decades. Despite plausible biological mechanisms and evidence from laboratory studies, findings from clinical research are conflicting. The objective of this study was to examine the association between PTSD and various cancer outcomes.

Methods—This nation-wide cohort study included all Danish-born residents of Denmark from 1995 – 2011. The exposure was PTSD diagnoses (n = 4,131). The main outcomes were cancer diagnoses including: 1) all malignant neoplasms; 2) hematologic malignancies; 3) immune-related cancers; 4) smoking- and alcohol-related cancers; 5) cancers at all other sites. Standardized incidence ratios (SIR) were calculated.

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Results—Null associations were found between PTSD and nearly all cancer diagnoses examined, both overall (SIR for all cancers = 1.0, 95% confidence interval (CI) = 0.88, 1.2) and in analyses stratified by gender, age, substance abuse history and time since PTSD diagnosis.

Conclusions—This study is the most comprehensive examination to date of PTSD as a predictor of many cancer types. Our data show no evidence of an association between PTSD and cancer in this nationwide cohort.

Keywords

stress disorders; posttraumatic; neoplasms; cohort studies

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a prevalent public health problem associated with significant costs to individuals and society.(1) Cancer, as a potential sequelae of chronic or severe stress, has been discussed in scientific publications during the past seven decades and even longer in historical literature.(2–4) Biological mechanisms proposed for this association include impairment of immune system function resulting from stress, which could impact the body's ability to fight tumor growth; alterations in DNA repair, which could promote cancer-related mutations; and the possibility that stress-related hormones play a role in tumor growth.(3, 4) Behavioral mechanisms have been proposed as well, most notably that stress precipitates behaviors that are risk factors for cancer (*e.g.*, smoking, alcohol misuse).(4)

Given the plausible biological mechanisms for this association, stressful events and cancer have been the subjects of much clinical research. Early small case-control studies reported an association of stressful life events with breast cancer and gastric cancer. (5–8) In the Finnish Twin Study (one of the largest studies to date), which combined self-reported data and medical records, specific acute stress events (*e.g.*, death of a husband) were associated with incidence of breast cancer.(9) A population-based study in Denmark found smoking-related malignancies among mothers to be weakly associated with loss of a child.(10)

Despite the few studies that have found associations between stress and cancer and despite the plausible mechanisms proposed, the majority of studies have found no evidence supporting an association.(4) Population-based studies of the association between stress and breast cancer have had null findings.(11) Job stress was not associated with breast cancer risk in the Nurse's Health Study. (12) A Danish population-based study found that cancer in a child (as the stressor) was not associated with a variety of forms of cancer among parents. (13) Most recently, a population-based study using registry data from Western Australia found no increased incidence of any type of cancer among persons diagnosed with stress or anxiety disorders, compared with the general population.(14)

Research to date is limited by a focus on specific stressful events or selected cancer types, which may explain the inconsistent findings. A recent review of studies of various forms of stress and breast cancer, encompassing epidemiology and molecular biology, called for well-designed cohort studies to elucidate these potentially important associations.(15) We know

of no population-based study that has examined posttraumatic stress disorder (PTSD)--the diagnosis given following exposure to a traumatic life event[1] --as a risk factor for diagnoses of many types of cancers. The current study fills this important gap in the literature by examining the incidence of various forms of cancer in a nationwide cohort of patients with a prior diagnosis of PTSD. Given the ubiquity of PTSD and cancer and their costs to individuals and society,(1, 16) any observed associations could have meaningful public health implications.

METHODS

We conducted a cohort study using Danish national administrative and healthcare registries to compare the incidence of various forms of cancer among patients with a recorded PTSD diagnosis with that expected in the general population during the same time period. The cumulative base population consisted of Danish-born residents of Denmark from January 1, 1995 through December 31, 2011 (80,607,865 person-years of follow-up).

Data Sources

The Danish Civil Registration System (CRS) contains a unique personal identifier (the central personal registry (CPR) number), date of birth, gender, and additional demographic data for all persons residing in Denmark since 1968.(17) The CRS contains data on vital status and address changes for each resident and is updated daily. The CPR number can be used to link data across all Danish administrative and medical registries.

The Danish Psychiatric Central Research Registry has collected data on inpatient hospitalizations since 1969 and outpatient psychiatric treatment since 1995.(18, 19) It contains treatment dates and up to 20 diagnoses per treatment episode for patients who are admitted to a psychiatric inpatient hospital, receive outpatient care, or are treated in a psychiatric emergency unit.(18, 19) We used the Psychiatric Central Research Registry to create a cohort of all Danish residents with at least one incident ICD-10 diagnosis of severe stress or adjustment disorder from January 1, 1995 to December 31, 2011.(20) Patients with PTSD diagnoses (see Appendix 1 for ICD-10 codes) within that cohort were used for the current study (n = 3143). Validation studies of diagnoses in the Registry (*e.g.*, schizophrenia and affective disorders) have shown high validity measured against computer-generated diagnoses or independent re-interviews.(18, 19) Our own validation study showed that validity is high for PTSD diagnoses recorded in the Psychiatric Registry.(21)

The Danish National Registry of Patients (DNRP) covers all inpatient non-psychiatric hospital treatment in Denmark since 1977 and outpatient and emergency room visits since 1995.(22) Its data were coded according to ICD-8 from 1977 through 1993 and ICD-10 thereafter. We used data from the DNRP to compute a Charlson Comorbidity Index (CCI) score for each patient in our study as a measure of overall physical health status.(23) As well, diagnoses of substance abuse were obtained from the DNRP and used to stratify our

[1]Additional ICD diagnostic criteria for PTSD include the traumatic event being exceptionally threatening or catastrophic in nature, which is likely to cause pervasive distress in almost anyone; persistent re-experience of the event or distress when exposed to reminders of the event; avoidance of things associated with the event; and symptoms of hyperarousal, all within six months of the event.

analyses (see Appendix 1 for corresponding ICD codes). Patients with PTSD diagnoses in the DNRP only were also included in the current study (n = 988).

The Danish Cancer Registry (DCR) has recorded all incident cancer diagnoses in Denmark since 1943. Diagnoses have been coded according to the ICD-10 since January 1, 2004 and all cancer diagnoses which were coded according to ICD-8 prior to 2004 have been recoded using ICD-10 codes.(24) Validation studies have found that 95% to 98% of records contained in the DCR are valid.(24) We obtained the following cancer diagnoses from the DCR: 1) all malignant neoplasms; 2) hematologic malignancies (*e.g.,* Hodgkin's lymphoma); 3) immune-related cancers (*e.g.*, liver cancer including cancer of the intrahepatic bile ducts, cervical cancer); 4) smoking- and-alcohol related cancers (*e.g.*, lung, colon, bladder); 5) cancers at all other sites (*e.g.,* ovary, fallopian tube, breast). Appendix 1 lists individual incident cancers and corresponding ICD-10 codes.

Analyses

We calculated the expected number of incident cancer cases after PTSD diagnoses using national rates of incident cancer diagnoses (restricted also to the Danish-born population of Denmark) according to sex, 5-year age groups, and 5-year calendar periods. Multiplying person-years of follow-up by incidence rates yielded the number of cancer cases that would be expected if persons with PTSD diagnoses had the same risk of cancer as the general population.(25) We calculated standardized incidence ratios (SIRs) to measure the association between PTSD and cancer as the ratio of observed to expected cancer cases. Confidence intervals (CIs) were calculated assuming that the observed number of cases for a specific cancer follows a Poisson distribution. Exact confidence limits were calculated when there were fewer than 10 observed cancer cases; otherwise Byar's approximation was used. Our presentation of results is limited to cancers for which there were 5 or more observed incident cases among persons diagnosed with PTSD during the study period. Presentation of stratified results is also limited to cancer diagnoses with at least 5 incident cases among people with PTSD within each subgroup.

We restricted our analyses to cancers diagnosed one or more years after the PTSD diagnosis date to ensure that the PTSD diagnosis was not linked to the cancer diagnosis. We further restricted our analyses to adults, defined as being age 16 or older. Analyses were stratified by time interval between first PTSD diagnosis and incident cancer diagnosis (1 to <5 years and 5+ years), sex, age at PTSD diagnosis (16 –39 years, 40 – 59 years, and 60+ years), substance abuse diagnoses, and CCI score. All statistical analyses were conducted using SAS version 9.2. The study was approved by the Danish Data Protection Agency (record no. 2012-41-0841) and by the Institutional Review Board at Boston University.

RESULTS

We identified 4,131 adults with a diagnosis of PTSD who had not had a cancer diagnosis one year after their PTSD diagnosis (60% female). PTSD patients were followed for an average of 7.6 years (median follow-up: 6.7 years; range: 1 year through 17 years). Age at PTSD diagnosis ranged from 16 years through 94 years (mean age: 39.4 years; median age:

39 years). Among PTSD patients, 159 cases of cancer were diagnosed one or more years after the PTSD diagnosis.

Table 1 displays associations between PTSD and incidence of cancers in major groups and for specific cancers. An overall null association was found for PTSD and cancer diagnoses (SIR = 1.0, 95% (confidence interval) CI = 0.88, 1.2). Null associations (shown in Tables 1 and 2) were also found for PTSD and all immune-related cancers (SIR = 1.0, 95% CI = 0.77, 1.4); non-melanoma skin cancer (SIR = 1.2, 95% CI = 0.88, 1.6); all smoking and alcohol-related cancers (SIR = 0.99, 95% CI = 0.72, 1.3); lung, bronchial and tracheal cancers (SIR = 1.3, 95% CI = 0.73, 2.0); colon cancer including cancer of the rectosigmoid junction (SIR = 0.59, 95% CI = 0.19, 1.4); cancer at other common sites (SIR = 1.1, 95% CI = 0.87, 1.5); breast cancer (SIR = 1.2, 95% CI = 0.82, 1.7); and uterine cancer (SIR = 1.4, 95% CI = 0.46, 3.3). No meaningful differences in this association were noted in stratified analyses (Table 2).

Effect of overall health

PTSD did not confer any additional risk for overall cancer incidence among persons with at least one comorbidity (as indicated by a CCI score of 1 or greater). The SIR among those with 1+ comorbidities was 0.60 (95% CI = 0.36, 0.95), while the SIR for those with no comorbid diagnoses was 1.1 (95% CI = 0.95, 1.3).

DISCUSSION

This nationwide cohort study -- the largest to date examining PTSD as a risk factor for a number of cancer outcomes -- showed no evidence of associations. This is consistent with other population-based studies, which reported that stressful life events are generally not associated with cancer incidence.(11–14) In addition to corroborating results of other studies, our large population sample enabled us to conduct important stratified analyses, which provided no strong evidence of associations among select subsamples.

Study strengths include use of data from a large population-based cohort with complete follow-up and little to no selection bias. As well, the large sample and long study period allowed us to examine associations that have not been studied previously. We were able to look at rare cancer outcomes and associations among important subgroups. In addition, we were able to examine validated PTSD diagnoses as a marker for prolonged clinically detected stress triggered by trauma from any source. Previous research has focused predominantly on specific stressful events.

Despite the size of the current study, it was too small to examine associations with rare cancers, particularly in the stratified analyses. Other limitations included an inability to adjust for behavioral risk factors for cancer, such as smoking. Future population-based studies are needed to replicate our results while incorporating these potentially important confounders.

In conclusion, our data shows no evidence of an association between PTSD diagnoses and various forms of cancer in a nationwide cohort overall or among particular population subgroups.

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Appendix 1. ICD Codes for Analytic Variables

	ICD Code
Posttraumatic stress disorder (PTSD)	F43.1
Substance abuse	ICD-8: 291, 303, 979, 980, 571.09, 571.10, 577.10 T36-T65, F10, G31.2, G62.1, G72.0, G72.1, I42.6, K29.2, K86.0, K70, R78.0-78.9, T51, Z72.1, Z71.4
Cancer Type	
Hematological cancers	
Hodgkin's lymphoma	C81
Non-Hodgkin's lymphoma excl. leukemia and myelomatosis	C82-85, C88
Multiple myeloma and malignant plasma cell neoplasms	C90
Leukemia	C91-C95
Malignant neoplasm of lymphoid, hematopoietic and related tissues, unspecified	C96
Immune-related cancers	
Liver including intrahepatic bile ducts*	C22
Malignant melanoma including those located in anus and anal canal (morphological code 872-879)	C43
Non-melanoma skin cancers	C44
Kaposi's sarcoma	C46, B210
Cervix	C53
Anus and anal canal excl. malignant melanomas (morphologic code 872-879) and basal cell cancers (morphologic code 809)	C21
External female genitalia excluding basal cell carcinomas (morphological code 809)	C51
Smoking- and alcohol-related cancers	
Lip	C00
Tongue	C01-02
Mouth	C03-06
Tonsil and pharynx	C09-C13
Other and poorly specified location in lip, oral cavity, and pharynx	C14

	ICD Code
Larynx	C32
Other and poorly specified location in airways and respiratory organs	C39
Esophagus	C15
Stomach	C16
Colon incl. rectosigmoid junction	C18-C19
Rectum	C20
Pancreas	C25
Lung, bronchus and trachea	C33-C34
Kidney	C64
Renal pelvis	C65
Ureter	C66
Urinary bladder	C67
All other sites	
Salivary gland	C07-C08
Small intestine	C17
Gallbladder and bile ducts	C23-C24
Other and ill-defined cancers of digestive organs	C26
Nasal cavity, middle ear and accessory sinuses	C30-C31
Thymus	C37
Heart and mediastinum	C381-383, C388
Pleura incl. mesothelioma pleura	C384, C450
Bone and articular cartilage	C40-C41
Mesothelioma	C45.1-C45.9
Peripheral nerves and autonomic nervous system	C47
Retroperitoneum and peritoneum, and malignant neoplasm of other connective and soft tissue	C48-C49
Breast	C50
Vagina excluding basal cell carcinomas (morphological code 809)	C52
Uterus	C54-C55
Ovary and fallopian tube	C56, C570-574
Placenta	C58
Other and unspecified female genital organs	C577-579
Penis excluding basal cell carcinomas (morphological code 809)	C60
Prostate	C61
Testis	C62
Other and unspecified cancers in male genital organs excluding basal cell carcinomas (morphological code 809)	C63
Other and unspecified urinary organs	C68
Eye and adnexa	C69
Meninges	C70
Brain including hypophysis, corpus pineale, and ductus craniopharyngealis	C71
Spinal cord, cranial nerves and other parts of central nervous system	C72
Endocrine glands and related structure	C73-C75

	ICD Code
Metastasis and unspecified cancer in lymph nodes (only if there is no primary tumor coded)	C77-79
Malignant neoplasm of other, ill-defined, or unspecified sites	C76, C80
Malignant neoplasms of independent (primary) multiple sites	C97

All codes ICD-10 unless otherwise noted.

Table 1

SIRs for selected incident cancers among patients with PTSD, Denmark, 1995 – 2011.

	Association with PTSD		
	Observed	**Expected**	**SIR (95% CI)**
All malignant neoplasms	159	154.4	1.0 (0.88, 1.2)
Any immune-related cancer	52	50.2	1.0 (0.77, 1.4)
Non-melanoma skin cancer	45	37.2	1.2 (0.88, 1.6)
Any smoking or alcohol-related cancer	42	42.3	0.99 (0.72, 1.3)
Lung, bronchial and tracheal cancer	17	13.6	1.3 (0.73, 2.0)
Colon cancer (incl. rectosigmoid junction)	5	8.4	0.59 (0.19, 1.4)
Other common cancer sites	61	53.8	1.1 (0.87, 1.5)
Breast cancer	32	26.6	1.2 (0.82, 1.7)
Ovarian and fallopian tube cancer	7	2.9	2.4 (0.96, 4.9)
Uterine cancer	5	3.5	1.4 (0.46, 3.3)

Table 2

SIRs for cancer one or more years after PTSD diagnosis, stratified by sex, age at PTSD diagnosis, substance abuse, and induction time.

	All malignant neoplasms	Any immune-related cancer	Non-melanoma skin cancer	Any smoking or alcohol-related cancer
Sex				
Female	1.0 (0.84, 1.3)	0.83 (0.54, 1.2)	0.95 (0.60, 1.4)	1.1 (0.67, 1.6)
Male	1.0 (0.79, 1.3)	1.4 (0.92, 2.1)	1.6 (1.0, 2.4)	0.93 (0.57, 1.4)
Age at first PTSD diagnosis, yrs				
16 – 39	1.2 (0.79, 1.6)	0.86 (0.43, 1.5)	1.5 (0.77, 2.8)	1.6 (0.52, 3.7)
40 – 59	1.0 (0.84, 1.3)	1.2 (0.84, 1.7)	1.2 (0.81, 1.8)	0.82 (0.52, 1.2)
60+	0.91 (0.60, 1.3)	0.72 (0.26, 1.6)	0.85 (0.31, 1.8)	1.3 (0.68, 2.1)
Substance abuse				
Yes	0.93 (0.56, 1.5)	1.0 (0.41, 2.1)	1.4 (0.56, 2.9)	1.6 (0.73, 3.0)
No	1.0 (0.88, 1.2)	1.0 (0.76, 1.4)	1.2 (0.83, 1.6)	0.90 (0.62, 1.3)
Time from PTSD to cancer diagnosis				
1 to < 5 years	1.1 (0.89, 1.4)	1.3 (0.83, 1.9)	1.5 (0.93, 2.3)	1.0 (0.60, 1.6)
5+ years	0.96 (0.77, 1.2)	0.88 (0.58, 1.3)	1.0 (0.66, 1.5)	0.97 (0.63, 1.4)

Note: Results not presented when fewer than 5 incident cancer cases were identified in a stratification subgroup